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A DECADE OF CARDIAC SURGERY*

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The present stream of cardiology is so broad that no physician or surgeon can claim to have mastered all its reaches. Since the simplest cardiac operation requires a knowledge of anatomy, physiology, pathology, and pharmacology, the anaesthetist and surgeon must be members of a team, the leadership of which must inevitably change from time to time.

Ten years ago surgeons thought they were entering a period of relaxation after three new technical procedures, initially difficult, had been mastered. Gross and Hubbard (1939) had established the need for and method of closing the ductus arteriosus, and Gross (1945) and Crafoord and Nylin (1945) had successfully operated on coarctation of the aorta. Blalock, having described with Helen Taussig (1945) his operation for increasing the blood flow to the lungs in congenital cyanotic heart disease, could record three years later the results of 610 operations performed for congenital cyanotic heart disease in the same year that the real surgery of the heart valves was initiated. Sellors (1948) and Brock (1949) performed the first direct operations on the stenosed pulmonary valve; Bailey, Brock, and Harken all operated successfully for mitral stenosis and opened the most successful chapter in the treatment of disability due to this disease since William Withering introduced digitalis.

The profession which had slept so long, nearly 25 years after Souttar's solitary successful effort to explore the mitral valve, suddenly awoke to the possibilities of surgery in this common disease. The time was ripe for a great surge forward: Forssmann's (1929) introduction of a cardiac catheter into the human heart had been applied by Cournand in America and MacMichael in this country to the study of pulmonary blood flows and pressures and of pulmonary hypertension: the haemodynamics of the circulation could be studied before and after operations on the mitral valve. But it must not be forgotten that the pioneer work of Brock, Bailey, and Harken was based on their obstinate belief in the surgical principle of relieving obstruction.

The rude shattering of the opinion that disease of the heart muscle accounted mainly for the symptoms in mitral stenosis has revivified cardiology and encouraged the study, by direct observation in the theatre, the radiological department, and the laboratory, of many cardiac disorders.

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I.—THE EVOLUTION OF SOME ESTABLISHED OPERATIONS

(a) Constrictive Pericarditis

By 1948 a working knowledge of this condition existed and many pericardiectomies had relieved the strangled heart and improved the diastolic filling of both ventricles. Most of us would regard the pericardiectomy of ten years ago as inadequate by present standards; attention has been paid not only to an anterior decortication of the ventricles but to liberating the posterior surface of the left ventricle and at times of the atria. Catheter studies usually demonstrate pulmonary hypertension of the type often seen in mitral stenosis, but the impairment of right ventricular filling by the disease process masks this clinically so that dyspnoea is not a severe symptom except in advanced, neglected cases. It is equally important to recognize the group with signs and findings on cardiac catheterization reminiscent of those of tricuspid stenosis, for extensive pericardiectomy over the right atrium and ventricle is necessary in this event.

* The main changes have been: (1) the earlier recourse to surgery even in the presence of active tuberculosis, streptomycin being the efficient watchdog of the infective side of the process; and (2) the tendency to carry on the clearing of the heart more and more to the left and to use an approach consisting of a bilateral thoracotomy with transverse division of the sternum. By this exposure a really adequate liberation of the heart in all areas is possible and safe. In ill patients presented late for surgery a less radical operation through a left antero-lateral transpleural approach is used.

(b) Persistent Ductus Arteriosus

By 1947 the diagnosis and surgical treatment of the uncomplicated ductus was established and few problems seemed to be left; but discussions have since ranged around the ideal age for operation, whether ligation or division is indicated (I practise division, as it fulfils surgical precepts; it is obligatory for the broad ductus), and the procedures to be employed when pulmonary hypertension has developed.

Age for Operation.—Increasingly more infants with heart failure due to a wide persistent ductus are being operated upon; dyspnoea, repeated lung infections, enlargement of the heart, with electrocardiographic

changes in infants who do not thrive from birth onwards, are the signposts indicating operation as a matter of urgency. In the symptomless group, the age of 3 to 4 years is a satisfactory time for surgery, as the technique of the operation is simple at that age, there is no interference with schooling, and the risk of pulmonary hypertension or of subacute bacterial infection is largely prevented.

It is curious that Maude Abbott's (1937) statistics, which showed that 48 of 242 deaths from a persistent ductus occurred in the first year of life, have received so little attention. The diagnosis at this age is not easy on clinical grounds alone: infants without cyanosis admitted in heart failure, with an enlarged heart with a systolic murmur only, may be suffering from coarctation of the aorta, ventricular septal defect, common atrioventricular canal, or a persistent ductus. Under medical treatment the infants with a ductus may convert this systolic murmur into a typical machinery one, but by no means always. In these infants, who may be only a few weeks old, cine-angiocardiography is safer than aortography in establishing the diagnosis. (Dr. R. Astley, my radiological colleague, kindly allowed me to show a film which illustrates the diagnostic points in left-to-right shunts in infants.)

In the 12 infants I have operated upon, the ductus has always been large and the typical lung biopsy appearance has revealed what Edwards (1955) regards as the foetal type of smaller pulmonary artery; these vessels show muscular hypertrophy and excess of elastic tissue. This "foetal" appearance is seen in other left-to-right shunts such as atrial septal defects that have caused pulmonary hypertension (Heath and Whitaker, 1957) but often show severe destructive changes when the shunt is of some duration.

These infants had severe lung symptoms with heart failure of varying degrees and transient cyanosis in five. The rapid restoration to health of the nine survivors suggests that, if pulmonary hypertension existed, it abated even when cyanosis had been present. This picture is very different from that seen in older children and adults with hypertension. If the flow of blood is balanced or has been reversed as a result of a steady increase in right ventricular pressure—the "atypical ductus" with a systolic murmur—the surgical problem is difficult. If the shunt is reversed to produce classical differential cyanosis, surgical closure will not reverse the changes in the irretrievably ruined lung vessels. In the only patient with this type of ductus on whom I have operated death followed 24 hours later. The pathological details of this case were published (Brewer, 1955). There was widespread occlusion of the pulmonary arteries by fibrous tissue, and many arteriovenous communications were noted. The real problem concerns those patients with a balanced or near-balanced shunt with pulmonary hypertension.

Ductal Occlusion in the Presence of Pulmonary Hypertension

Surgery can help some patients with hypertension. Such have large hearts, a systolic murmur, respiratory symptoms, and easy fatigability. Ziegler (1955) accurately delineates two types, and our experience confirms his grouping.

1. *Ductus Arteriosus with Moderate or Marked Pulmonary Arterial Hypertension and Increased Pulmonary Blood Flow.*—Here there is a capillary or post-capillary hypertension diagnosed by finding an elevated pulmonary "wedge" pressure by cardiac catheterization. The electrocardiograph often shows right ventricular hypertrophy and pulmonary hypertension of a predominantly diastolic type; urgent division of the ductus, which will be large, is indicated and the changes in the lung vasculature are reversible.

2. *Ductus Arteriosus with Marked Pulmonary Arterial Hypertension and Normal or Decreased Pulmonary Blood Flow.*—Because of permanent damage in the pulmonary arterial tree at the pre-capillary level the "wedge" pressure will not be raised, and this finding in a patient with right ventricular hypertrophy and a high pulmonary artery pressure is certain evidence of increased pulmonary artery resistance; radiologically the lung shows decreased pulmonary vascularity and the electrocardiograph invariably denotes severe right ventricular hypertrophy: the patient may be permanently cyanosed. Surgical occlusion is contraindicated.

Whenever operation is carried out on a ductus with a systolic murmur direct pressures are taken in the aorta and the pulmonary artery before the ductus is clamped and immediately after the clamping: if the pressure rises in the pulmonary artery in adults, the operation should be abandoned; in children, however, the clamp is left on for 15 minutes; if the right ventricle continues to behave well the ductus can be divided: such children usually have a difficult convalescence for the first few days but then recover steadily.

Much misunderstanding results from the statement that pulmonary hypertension contraindicates surgery in the treatment of left-to-right shunts such as ductus arteriosus or atrial or ventricular septal defects; what really is meant is that surgery is valueless when the pre-capillary vasculature has deteriorated so disastrously under an attitude of "wait and see" that the patient has entered the stage when reversal or balancing of the shunt is associated with marked pulmonary arterial hypertension but a decreasing pulmonary blood flow into the left atrium.

The Complicated Ductus

Operations on a typical uncomplicated ductus carry a low mortality rate. In my own series of 180 operations 141 were of this type, and there has been one sudden death two weeks after operation, when the patient was at home. The remaining 39 patients were complicated in various ways and the mortality rate was high, with 10 deaths (Table I).

TABLE I.—*Results of Surgery in 39 Complicated Cases*

	No.	Deaths	Ages
Infants with cardiac failure	12	3	1–23 months
Associated defects (V.S.D., A.S.D.,* coarctation, congenital mitral stenosis) ..	7	0	3–10 years
Cardiac failure or pulmonary hypertension	12	3	(4, 4, 6, 6, 11, 12, 23, 24, 38, 45, 47, 55)
Infected	8	4	(8, 11, 13, 17, 27, 30, 31)

* V.S.D. = Ventricular septal defect. A.S.D. = Atrial septal defect.

The "cardiac failure" deaths included three infants with severe pre-operative failure: one was an infant of 21 months who died seven days after surgery; a false aneurysm developed and ruptured into the left lung—an example of staphylococcal infection. A boy of 6 with great cardiac enlargement had been thought to have a ventricular septal defect for several years; the murmur was systolic, and there was right ventricular hypertrophy and pulmonary hypertension. The ductus was clamped for 15 minutes, and, as the right ventricle behaved well, the ductus was divided; he died the next day. Necropsy revealed an unsuspected gross mitral regurgitation due to fibroelastosis; there were advanced changes in the pulmonary artery, and the vascular obstruction was clearly pre-capillary. Another death was that of a woman of 24 with differential cyanosis, to whom reference has already been made—a further example of pre-capillary hypertension and really inoperable. The sixth death was in a man of 45 with increasing dyspnoea who at

operation had severe degenerative arterial changes: a tear occurred in the aorta which proved fatal.

Of the four fatal cases of subacute bacterial endocarditis one had a mycotic aneurysm of the left lung in addition to gross infection at the site of the ductus. The second was a girl of 17 with heart failure in addition to the infection; she had a large ductus which I ligated (it should have been divided): recurrence followed, and two further attempts were made to close this ductus, at the last of which fatal haemorrhage occurred. The third was a child of 8 who, in addition to the infected ductus, had syringomyelia and tuberosclerosis. The last case, a boy of 11, had gross infection of the pulmonary artery and was an operative fatality.

Division of the Ductus in the Presence of Associated Anomalies

If a ductus is associated with a post-ductal coarctation of the aorta there can be no doubt that surgery at an early age to correct both defects is indicated: the delivery of the extra blood from an aorta in which the pressure is abnormally high increases the risk of early pulmonary hypertension. A persistent ductus is said to be present in 10% of patients with coarctation of the aorta.

It is in combination with other cardiac abnormalities, such as septal defects, that ductal occlusion, though helpful, is clearly not the full solution. After studying sizes of hearts before and after ductal occlusion on many patients it was noted that the size decreased in all but five: these all had associated septal defects, and, although the children are well, their future cannot be regarded without anxiety, and the possibility of their being operated on to close the defects by open cardiotomy is being considered. If infants with severe symptoms and a proved ductus have an associated septal defect, closure of the ductus alone may be life-saving.

In two children a large ductus has been associated with congenital mitral stenosis. These have been described (Bower *et al.*, 1953). One child who was in severe respiratory distress survived mitral valvotomy and is still alive and well four years later, though far from cured. At the operation pressures were taken in the aorta and pulmonary artery before and after temporary clamping of the ductus; this occlusion caused a steep rise in pulmonary artery pressure. The left atrium was then explored and a congenitally tight mitral stenosis opened: the pressures in the pulmonary artery, however, still showed a rise when the ductus was temporarily occluded; it was not divided, as it clearly served a function in lowering the pressure in the lung vessels. The second child who was operated upon died: extensive changes in the heart characteristic of fibro-elastosis were found at necropsy.

(c) Coarctation of the Aorta

In the management of classical coarctation of the aorta (the post-ductal or adult type) opinion has steadily veered towards the surgical view that good relief of the aortic obstruction will lower the blood pressure and prevent the more disastrous complications of this condition. No one, however conservative, doubts the malignancy of coarctation in most patients, and no one is ignorant of the fact that a few survive to a good age. Maude Abbott (Hamilton and Abbott, 1928) found that in 71% of 200 necropsy cases the patients had died before the age of 40. Reifenstein *et al.* (1947) found that 61% of his 104 patients suffered the same fate; in my own experience I have not seen any patients over the age of 40 without considerable symptoms, of which exertional dyspnoea has been the outstanding one. As the operation has been in wide use only since 1950 it is impossible to say whether it will prolong life. Since the mortality rate has been steadily lowered most cardiologists regard the risks of the natural course as being higher than those of surgery. During the developing stages of any major operation not only is technique hesitant but bad-risk patients are submitted.

In my own small series of 51 operations there have been five deaths: those of an infant, a girl of 17 with a large ductus who died at a second-stage operation in a technically mismanaged case, two young men (deaths being due to haemorrhage, one post-operatively, attributable to my technical imperfections), and a man of 50 with large intercostal aneurysms, uncontrollable haemorrhage occurring from the rupture of an aneurysm of the bronchial artery.

Gross (1953) reported that in his first 270 operations there were 15 deaths in the first 100 but only two in the last 100. Since operation is being advocated increasingly at ages between 6 and 10 (d'Abreu and Parsons, 1956) the mortality rate is falling sharply, the surgical procedure being simple in children and the convalescence rapid. Operation in childhood and early adolescence, when the aortic tissues are free from degenerative changes, seems to be the best way of avoiding complications such as subacute bacterial infection, the development of intercostal aneurysms (I have seen these at the age of 16), dissecting and non-dissecting aneurysms of the aorta, heart failure, and the effects of hypertension such as cerebral haemorrhage, often due to the rupture of berry aneurysms at the base of the brain.

Effect of Surgical Excision and Anastomosis on the Hypertension

If an anastomosis of good calibre is obtained, a fall in blood pressure in the arms and a development of good pulsation in the lower limb vessels will follow; the fall of brachial artery pressure may not be down to the normal of corresponding age groups (Cleland, 1955), but its lowering must surely be better than the acceptance by the patient of a hypertension that usually rises with the years. In children the falls in pressure are more satisfactory and far more immediate than in adults, though, as in them, the fall continues over the 18 months following operation.

In a boy of 14 with very large collaterals the result was bad, although I thought the anastomosis was a good one. Two years later aortography showed, in fact, narrowing at the anastomosis site; I reoperated on him, excised the strictured area, and inserted an aortic graft; this was followed by satisfactory lowering of the blood pressure.

In infants cardiac failure occurs quite often; in five years at the Birmingham Children's Hospital, Parsons (1955) found 30 deaths in infancy. With adequate medical treatment the infant may be tided over the failure, and, as Gross maintains, surgery can then be postponed. If, however, the condition continues to deteriorate surgery should be employed; disappointment may follow the operation, which is a simple one in infants, but, in my experience, has enabled four out of five infants to survive. Unfortunately fibro-elastosis is not an unusual concomitant. A coarctation with a ventricular septal defect has been resected in two, with survival.

The Lesser Circulation in Coarctation

Parsons in following up children after resection of coarctation has been struck by the constant insistence of the parents and children themselves that breathlessness has been abolished: this in spite of the fact that pre-operatively no mention had been made of dyspnoea. Recently Donald and Taylor, in Birmingham, have investigated the haemodynamics of the circulation before and after surgery, and their results will be published shortly. They have found evidence that a raised pulmonary capillary pressure in coarctation before operation has fallen to normal when measured six months or more after excision of the coarctation. It is also clear on purely clinical grounds that many children with pure coarctation have unexpected right ventricular strain.

Relief of Symptoms after Excision of Coarctation

Cleland *et al.* (1956), in reporting fully on 37 patients after operation, found them all in good physical condition with no recurrence of their symptoms. In 44 of my own patients, adequately followed up, I have found the same. In

children, symptoms are by no means infrequent. Parsons on following up 11 children found that 5 with pre-operative headache, 8 with abnormal feelings of exhaustion after exercise, and 2 with intermittent claudication had complete relief after surgery in addition to the abolition of dyspnoea, already mentioned.

At the moment, surgery is indicated in coarctation of the aorta in the early years of life (5–16), when a low mortality rate can be expected: the objection that the aorta will not enlarge with the growth of the patient has not been confirmed by laboratory experiments or by aortography done years after the resection in this group of patients.

Better anaesthesia with the use of hypotension produced by trimetaphan camphorsulphonate ("arfonad") for short periods during the excision and the anastomosis, the use of Potts's small-toothed aortic clamps, and Brom's approximating device have removed many technical difficulties. In all large centres the easy access to dry-frozen homografts has provided an extra source of confidence, though their use is rarely required in children and young adolescents; they have a wider place in adults whose complications, such as rigidity of the aorta and aneurysmal formations, occasionally make their use imperative, and they must be available in the theatre at every operation.

(d) Mitral Stenosis

By clinical and physiological measurements a well-performed operation on a valve with a critical degree of stenosis (1 cm.) relieves the dyspnoea and improves the haemodynamic picture of the circulation, especially on the pulmonary side. Since the operation has been practised widely for less than ten years the effect on the expectation of life cannot be assessed, but the quality of many lives has been dramatically altered.

From a clinical follow-up of the first 300 patients personally operated upon (Table II) the results are excellent in those with pure mitral stenosis, well compensated and in

TABLE II.—*Results of 300 Mitral Valvotomies*

Normal rhythm:				Fibrillation:			
Cases			166	Cases			134
Deaths			5 (3%)	Deaths			10 (7·5%)
Age	Cases		Deaths	Age	Cases		Deaths
10–19	11		0	40–49	85		8
20–29	59		1	50–59	19		3
30–39	126		3				

Eight deaths occurred among the first 100 patients, five among the second, and two among the third.

normal rhythm with pulmonary hypertension; they are good in similar patients with atrial fibrillation. The poorest results are in fibrillation with gross pulmonary hypertension and congestive failure. But it must be remembered that in this last, unpromising group startling results are occasionally obtained, and they should not be rejected lightly as candidates for surgery. If there are permanent severe changes in the smaller pre-capillary vessels the results, as discussed earlier in relation to the ductus arteriosus, will be bad, as the obstruction is no longer confined to the left atrium but is largely in the wrecked pulmonary artery system.

Most of the published studies of patients three or more years after operation concern those done in the early years of mitral surgery when the valvotomies were less thorough than those of to-day; none the less, all reports are remarkably consistent, with successful results of between 75 and 80%. In all centres patients are coming in small numbers with "re-stenosis" having taken place. I have had to re-operate on five patients, whose primary valvotomies were done three to six years ago. Although my own operation note on these showed that I was satisfied at the time with the valvotomy, to-day such an operation would not be regarded as really sufficient. As in all operations, experience leads to more thorough procedures, and this is so in mitral surgery. Re-stenosis occurs particularly when the valve mobility is poor, however good the split in the commissures. Re-stenosis is certainly a problem, but I doubt if it will be a large one provided the original operation is thorough and a valve with mobile cusps is left after the splitting has taken place.

In the follow-up the bigger the size of the reopened valve the better has been the result; the poorest results, apart from grade IV patients, have been with heavily calcified valves, or where a funnel-shaped type of left atrium has led down to a stenosed orifice surrounded by cusps with shortened, thickened chordae tendineae.

The 300 patients were not all suffering from pure mitral stenosis, but it has been regarded as the predominant lesion: there were 15 hospital deaths, a mortality rate of 5%: in the last 100 cases there were two deaths, both fibrillators and both over the age of 40. It is a comfort to be able to tell prospective candidates for surgery in the age group 20–39 that the mortality risk is under 2% and that if they are not fibrillating it is under 1%.

Optimal Time for Surgery

Many patients are still being referred for surgery after the best time has passed. In the present series 11 of the 15 deaths were in patients over the age of 40. Surgery should be considered in all patients with progressive symptoms. When doubt exists about the severity of the symptoms (often underrated by a patient used to dyspnoea), if cardiac catheterization shows evidence of right ventricular overwork, a fixed cardiac output, a raised pulmonary artery and wedge pressure, and increased ventilation and high oxygen uptake, then surgery is indicated. From a clinical assessment of these 300 patients, of the surviving 285 very good results have been obtained in 70%, great improvement in 10%, and the remainder (20%) have deteriorated or died, mainly from progressive cardiac failure. These results are very similar to those reported by Turner and Fraser (1956) in a progress report on the first 250 valvotomies performed in Logan's clinic in Edinburgh, by Mounsey (1957) on the results of 100 from the London Hospital, and in many other reports throughout the world.

Post-operative Changes in Circulatory Haemodynamics

Many studies of pre- and post-operative states have been published; I am quoting only from the studies of Donald and his colleagues (1957), because I am more conversant with their work and because their complete studies have not been widely read and are possibly unique in their thoroughness. In a study of 24 patients with clinically satisfactory results the striking changes were in the lungs. Ventilation at rest and on exercise was greatly reduced in most; the resting oxygen uptakes fell to normal in all but one, and this indicates the decreased work done on breathing. The mean pulmonary arterial pressure at rest fell after operation in all except two, but remained abnormally high on exercise. The pulmonary capillary wedge pressure was lowered in all; this, together with the decrease in ventilatory work and the loss of Kerley's lines (probably due to lymphatic fluid around the pulmonary veins), points to a relief in the post-capillary pressure in the lung vessels. The wedge pressure, however, still becomes elevated on exercise even in patients without clinical disability. The work of the right ventricle was greatly reduced to within normal limits. All these changes were present with no great increase in the cardiac output.

Changes in Technique

Reduction in the amounts of anaesthetic and relaxant drugs used, and the immediate correction of hypotension at any stage of the operation by small doses of noradrenaline run in through a separate intravenous infusion set, have much increased operative safety.

Increasing insistence on obtaining a really wide valve opening has meant that more instrumental valvotomies are being done if a purely digital commissurotomy is inadequate. Dubost (1955) has had excellent results by using a dilator

which is placed in the mitral orifice through the atrial appendage; Logan has, I believe, made this procedure safer and more effective by introducing a dilator through a tiny stab wound in the left ventricle: with the finger of the right hand in the left atrium the dilator is guided from below to lie accurately in the valve orifice so that it can be opened using bimanual control; it produces excellent splitting of both commissures. My own practice now is to attempt to divide the commissures with a Vernon Thompson finger-ring knife. If this fails I proceed to Logan's method. The latter method is of especial value when a large organized intra-atrial thrombus prevents the use of the atrial appendage for digital entry into the heart; the little finger is then introduced through a pulmonary vein or a small incision in the atrial wall, guarded by a purse-string suture, and the dilator passed through a left ventricular incision to be guided into place by contact with the little finger above the valve.

Management of Patients with Intra-atrial Clots

Patients with the indications for valvotomy who have had previous embolic episodes should on the whole be subjected to operation; in this series 30 patients with previous embolisms have undergone valvotomy with one post-operative embolism. The main cause for anxiety in a mitral valvotomy is the risk of post-operative embolisms; this risk is almost but not quite confined to fibrillators. At operation the atrial appendage should be opened before the atrial clamp is applied firmly, so that the gush of blood through the lips of the incision will wash away loose clots; temporary clamping of the branches of the aortic arch before and during any manipulations within the atrium may be indicated, and Barrett (personal communication) has found this to be extremely effective; I have, however, had two cerebral embolisms after very careful occlusion of the innominate and left carotid artery and can give no considered opinion on the value of the procedure, nor on the use of anticoagulant therapy which has been used in most of the fibrillators in this series.

When a large organized clot is present in the atrium it may be possible to remove it, but access to the mitral valve may have to be made around or under it via incisions in the atrial wall or through a pulmonary vein. A ball thrombus can be removed by a separate incision in the atrial wall through which it is levered out into and through the incision in the atrial appendage. The removal of these massive clots may possibly be better undertaken by the use of open cardiac surgery.

(e) Aortic Stenosis

In the past ten years the surgical relief of aortic stenosis has lagged behind that of mitral stenosis. In mitral stenosis relief can be afforded long before the patients are bad operative risks, however severe the symptoms. This is not so with aortic stenosis; deterioration when it comes is sudden, indicating a left ventricle in sad trouble; to await these symptoms is to find a patient with a short expectancy of living. In addition to this sudden clinical deterioration the recognized heavy calcification in many of these valves and the risk of producing incompetence have been factors inducing caution. Bailey (1955) pointed out that aortic valvotomy in a patient who also had established mitral stenosis is a far safer procedure when carried out concurrently with mitral valvotomy than in patients with pure aortic stenosis, since the mitral stenosis has protected the muscle of the left ventricle. If the gradient of pressure across the aortic valve is 50 mm. Hg or over with associated mitral stenosis, the aortic valve can safely be tackled at the same operation. Similarly, if a stenosed aortic valve with this sort of gradient can be opened without producing incompetence and before the left ventricular muscle has been overtaxed, the mortality will be below 10%.

In recent years new methods have enabled the cardiologist to know exactly the gradient across the aortic valve: for example by left atrial and left ventricular catheterization effected by passing a fine catheter through a cannula introduced into the left atrium through a bronchoscope (Allison and Linden, 1953), by direct transthoracic atrial puncture (Björk, 1954), and by direct percutaneous left ventricular puncture (Brock, 1956). The last method is safe and can be carried out with a needle of moderately large bore, which cuts down damping effects. By this method surprisingly high pressures are disclosed in left ventricles even in children. Patients with classical aortic stenosis and a systemic blood pressure of over 120 may have a left ventricular pressure of 250–300; in one child of 12 with apparently minimal symptoms, though these included a genuine attack of coronary pain, a ventricular pressure of 250 was found, which after valvotomy fell to 140; more and more patients are being presented for surgery.

The technique of aortic valvotomy is a controversial subject. Bailey developed the transaortic approach, a patch of pericardium or plastic material being sutured to the lips of an incision in the ascending aorta; through this pouch digital and instrumental relief of the obstruction can be carried out, probably more accurately than through a ventricular incision into which is introduced a sound and a dilator. The transaortic method is more difficult technically than the use of a Brock dilator through the left ventricle. This instrument, properly used, need not produce incompetence, as the commissures, here as in the mitral valve, tend to split along the natural line of pathological fusion. The heavily calcified valve presents a problem of great difficulty, and operation in this type will naturally carry a greater risk of incompetence than operation on a valve with only fibrous fusion.

I have found satisfactory direct-vision surgery through an incision in the aorta under hypothermia with the venous inflow to the heart occluded and the aorta clamped off above the incision site (to prevent air embolism). I believe it is the safest method of dealing with the calcified valve. The important point is to think of surgical relief before the patient has degenerated into a severe surgical risk. At the moment a mortality risk of 5% in good-risk patients can be offered; if, as should be done on occasion, cardiac cripples with large left ventricles and anginal pain are accepted, a mortality rate of 40–50% is the rule.

(f) The Tricuspid Valve

Isolated tricuspid stenosis is rare; incompetence, usually functional, with mitral stenosis is not uncommon: tricuspid atresia can be diagnosed accurately by modern methods and can be dealt with through the right atrium. It is not such an easy valve to open as the mitral valve because of its three cusps. If associated with mitral stenosis it is often wiser to deal with the mitral valve and await the result of this and a further catheter assessment of the haemodynamics before embarking on the tricuspid valve.

Evidence of mitral stenosis with oedema but without real lung symptoms or a plethoric lung should lead to suspicion, especially if the oedema persists after a good mitral valvotomy: vigorous pulsation in the neck, with cyanosis, a large right atrium, and a lower diastolic murmur at the lower end of the sternum, suggest the diagnosis. The cardiac catheter will show characteristic pressure changes.

Changes in Attitude to the Heart

The success of operations on the ductus, the coarcted aorta, mitral stenosis, and in congenital cyanotic heart disease have shown that severely crippled hearts can stand up to long interventions under good anaesthesia. Anaesthesia has become lighter and lighter, with minimal doses of the drugs required to give relaxation and unconsciousness. Hyperventilation with full oxygenation prevents acidosis.

Firm manipulation of the heart without untoward results has convinced us, perhaps belatedly, of the truths taught us in physiology that the heart muscle is powerful, adaptable, and elastic; it will stand tourniquets applied to its inflow and outflow great vessels under hypothermia or with an extracorporeal circulation; when arrested chemically by

the potassium citrate method of Melrose (1953) its metabolism is so damped down that open surgery can be carried out for periods of well over 20 minutes. It will even recover after gross air embolisms into the coronary arteries.

The modern treatment of cardiac arrest is established. The direct transthoracic approach alone provides sufficient access for cardiac resuscitation in which the two main essentials are full lung oxygenation and manual massage sufficient to provide an easily palpable pulse in the carotids. Whether the heart is in complete asystole or in ventricular fibrillation the circulation to the brain must be maintained by manual compression for several minutes before recourse is made to drugs or to undertaking defibrillation. The method of defibrillating the heart by one or more powerful electric shocks is now effective, and no hospital to-day can be without its defibrillator. Of the drugs used, direct intracardiac adrenaline and calcium chloride are the most valuable.

Exposure of the Heart.—For procedures such as blind mitral, aortic, pulmonary, or tricuspid valvotomy, good exposure can be obtained through one pleural cavity (Fig. 1). In the last few years, however, increasing use has been made of bilateral thoracotomy with transverse section of the sternum. This exposure is necessary for open cardiotomy under hypothermia or to establish an extracorporeal circulation, and with the heart so exposed all areas can be examined fully (Fig. 2).

FIG. 1.—Exposure of the heart through left transpleural approach. This exposure is adequate for mitral valvotomy, blind pulmonary valvotomy, and blind aortic valvotomy. It is inadequate for open cardiac surgery.

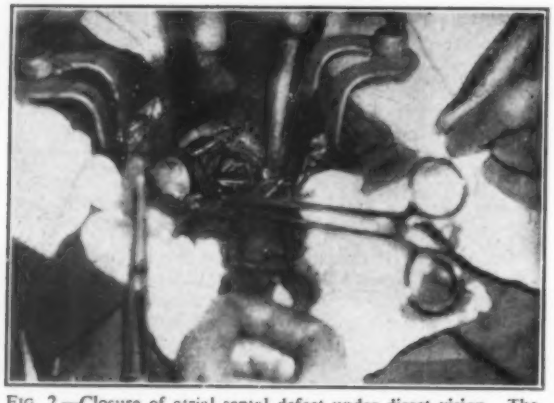

FIG. 2.—Closure of atrial septal defect under direct vision. The heart has been exposed by a bilateral anterior thoracotomy with transverse division of the sternum. The superior and inferior venae cavae have been occluded by tapes passed through rubber tubing. The aorta and the pulmonary artery have been occluded by a clamp passing through the transverse sinus posteriorly. The right atrium has been opened and the septal defect is being sutured.

II.—DISSATISFACTION WITH BLIND PROCEDURES

At operation for mitral stenosis a careful assessment of the valve cusps, the size of the valve orifice, and the state of the chordae tendineae and their attachments can be made. It is difficult to imagine the discarding of this "blind" operation for open cardiotomy in mitral disease. Attention is being focused on the possibility of open surgery in mitral incompetence which, it seems to many of us, only very careful plastic surgery can correct.

In addition to thousands of successful mitral valvotomies and many aortic valvotomies, relief of pulmonary valvular and infundibular stenosis, and the blind occlusion of atrial septal defects, have been achieved. It is with special reference to open surgery in pulmonary stenosis and atrial septal defects that I wish to speak. In his Simpson Smith Memorial Lecture of 1949 and in his latest book, Brock (1957) has described fully the anatomy of obstruction to the outflow track of the right ventricle; by resecting tissues causing obstruction to the infundibulum of this ventricle and by division and dilatation of a stenosed pulmonary valve by ingeniously designed instruments he proved that the pressure across these areas of congenital obstruction could be altered drastically; the results have continued to be good. In pure pulmonary valvular stenosis without ventricular septal defects most to-day would agree that evidence of right ventricular strain is an urgent indication for surgery. All cardiac surgeons have done this operation blindly; many have been disappointed to find months later that, though catheter evidence shows a decrease in right ventricular pressures and an increase in that in the pulmonary artery, the right ventricle shows persistence of hypertrophy: for this reason many of us prefer open valvotomy through the pulmonary artery, first performed by Swan (Swan *et al.*, 1953). This can be done safely under hypothermia at a temperature of 29–30° C., but naturally requires a wider thoracotomy than in Brock's operation.

Atrial Septal Defects

The frequency of this anomaly, at times associated with aberrant pulmonary veins draining into the right atrium and with pulmonary stenosis, and the usual clinical deterioration of the patient between 25 and 40, make the problem of surgical correction an important one. Campbell *et al.* (1957), after a full review of 100 patients, think the prognosis is rather worse than in ductus arteriosus. Reasonably good closure has been produced by sewing part of the redundant invaginated atrial wall to the edges of the defect, the suturing procedure being guided by a finger introduced into the right atrial appendage (Bailey *et al.*, 1953; Edwards *et al.*, 1955) or by the Sondergaard (1955) operation, in which a circumferential suture, accurately placed, approximates the anterior to the posterior wall of the defect. Another method, that of Gross (Gross *et al.*, 1952), consists in the use of a "well" sutured to an incision in the atrial wall through which, by digital contact, the defect is sutured or closed by the sewing in of a patch of plastic material: this method has been used extensively and safely by Kirklin, of the Mayo Clinic.

These methods, which are by no means discarded, have the usual drawbacks of blind surgery, and closure under direct vision under hypothermia is surgically more satisfying. None of the methods is applicable to that variation of atrial septal defect known as "the ostium primum defect" or "the persistent common atrio-ventricular canal." In this complicated anomaly there is a deficiency low in the atrial septum which involves also the top of the ventricular septum and is accompanied often by a cleft, incompetent mitral valve and sometimes by an incompetent tricuspid valve. Such a condition, which can be diagnosed accurately by correct interpretation of the E.C.G. and catheter findings, can be corrected only by open cardiotomy with an extracorporeal

circulation, as the time required for the plastic repair much exceeds that provided by hypothermia. Besides blind repair is futile if the anatomy of the abnormality as seen at open surgery or necropsy is remembered.

Surgical Closure of the Ostium Secundum Defect under Hypothermia

Only a few technical points can be mentioned here. The operation should be done before the persistent large ventricular output has caused right-sided heart failure or fixed pulmonary hypertension, and long before the onset of cyanosis (in the absence of pulmonic stenosis) has indicated a reversal of the shunt. The operation is done before symptoms are clamant. In a young patient the beneficial effects of closure can be seen while the patient is still on the operating table, and the obvious diminution in size of the right atrium and the right ventricle is one of the dramatic sights of cardiac surgery.

Bedford *et al.* (1957) and Sellick (1957) have published a lucid account of their technique, surgical and anaesthetic, in the closure of 40 atrial septal defects with two deaths, and this is largely based on the work of Swan (Swan *et al.*, 1953). Of the three methods of producing hypothermia, by veno-venous cooling (Brock *et al.*, 1956), by the blanket method (Inglis *et al.*, 1954), or by the method of immersion in a cold bath, they prefer the latter. I have used the blanket method and the cold bath, and find both satisfactory; the blanket method is less awkward and requires fewer people in the theatre for its management, but the rate of cooling is a little slower than by cold-bath immersion. As the temperature continues to drop as soon as the bilateral thoracotomy has been done, the operation can be started with the temperature between 30 and 31° C.

First the caval vessels are prepared for their temporary occlusion: it is important, however careful the pre-operative angiocardiographic and catheter studies have been, to look for two important associated abnormalities: (1) anomalous pulmonary veins draining into the superior vena cava or into the right atrium, and (2) supernumerary caval vessels. In one patient of 12 two superior venae cavae were seen, the left one as usual draining into the coronary sinus; and two inferior venae cavae, both fortunately draining into the right atrium. Sometimes the inferior vena cava, or an accompanying vessel, may drain wholly or partially into the left atrium. If a left superior vena cava is overlooked and not temporarily occluded during the cardiotomy a great volume of blood will flow into the coronary sinus and obscure vision.

Before the circulation into and out of the heart is occluded the right atrium is explored digitally to confirm the diagnosis. If the right ventricular pulmonary outflow tract or the pulmonary artery provides any appearance suggestive of stenosis, pressures should be taken in the right ventricle and in the pulmonary artery to estimate the gradient. Usually this diagnosis will have been made by pre-operative catheter or angiocardiographic studies. Should the stenosis be significant it is dealt with by open pulmonary valvotomy before the atrium itself is opened.

If an ostium secundum is present, the finger is withdrawn from the atrium, which is clamped; the circulation is then occluded by applying temporary compression to the caval vessels and the disappearance of the carotid pulsation is awaited: the aorta and pulmonary artery are then occluded with one large clamp, and the right atrium is widely opened by enlarging the previous incision made for the digital exploration. The blood having been rapidly sucked from the atrium, the defect, usually 2–5 cm. in length, sometimes with small secondary deficiencies, appears as a long slit which can be sutured with 000 silk (Fig. 2). Two sutures are used, each starting at the end of the defect; before these are tied together the anaesthetist exerts pressure on the lungs to drive blood on into the left atrium, which forces air from that chamber to the surface and out of the left side of the heart. This is further assisted by pouring into it saline, under which the sutures are then tied to each other; the temporary clamping of the inferior vena cava is released, and when the right atrium is full of blood the incision in its wall is held in a clamp and the occlusion of the superior vena cava relaxed. When the heart is full of blood the clamp on the aorta and pulmonary artery is opened; usually the heart, which has been beating regularly throughout apart from frequent fibrillation of the right atrium, returns to normal rhythm. Should the ventricle fibrillate, massage is employed before defibrillation is undertaken: the condition of the heart will often improve if warm saline is poured over it to raise the local temperature. The incision in the atrium is then closed by suture.

Criticism has been made of the use of a simple suture of the defect, and recurrence has been regarded as probable. At open operation, however, the walls of the defect come together without any tension, and I believe rapid adherence is the rule; time will show whether this assumption is correct: experienced surgeons such as Kirklin believe that the incorporation of plastic material is helpful.

The ease of right atrial cardiotomy can be made use of for the open surgery of the stenosed tricuspid valve, and, as Chin and Ross (1957) have shown, for the removal of a myxoma of the left atrium by an approach through the atrial septum.

Open Cardiotomy with Extracorporeal Circulation

Probably more time is being applied to this problem than to any other branch of surgery. The brilliant results that have followed the use of the Blalock–Taussig operations of anastomosing a systemic to a pulmonary artery, or of the Potts procedure in which the aorta is anastomosed side to side to the pulmonary artery, are undoubted; but, although after over ten years of follow-up most of the patients are satisfactory, the addition of an extra defect to the tetralogy has been accompanied in many cases by a steady increase in heart size. Brock's original direct attack on the infundibular or valvular stenosis in these patients led the way to a more physiological solution of the problems of pulmonary oligaemia, but he himself aways felt that the closure of the right-to-left shunt was the next essential step. Lillehei (Lillehei *et al.*, 1955) first achieved this by using cross-circulation from a human donor and then by the use of the bubble-oxygenator in combination with a venous and arterial "sigmamotor" pump.

As far back as 1937 Gibbon, of Philadelphia, was publishing the results of his work on a heart–lung machine, and his constant attention to the problem through years of work has led to the designing of the Gibbon–Mayo pump oxygenator, with which Kirklin has performed hundreds of open cardiotomies with astonishing success. The time has come when most surgeons are reluctant to carry out an anastomotic operation for congenital cyanotic disease except under conditions of great urgency, as when the state of an infant or child is grossly deteriorating, in which case the surgical relief of the pulmonary obstruction with simultaneous closure of the ventricular defect is the ideal. The anastomotic operation still has a place in conditions such as tricuspid atresia with an absent or diminutive right ventricle.

Ductoplasty.—The problem of the very young child with cyanosis who is deteriorating is an anxiety to many of us; many die before they are old enough to be subjected tc open cardiotomy or in centres where the extracorporeal circulation has not been established. If a Potts or a Blalock operation is done as an emergency measure a condition is established which may well make the later performance of open cardiotomy for correction of the defects difficult. In these circumstances it is permissible to use a human arterial graft to add a by-pass from the aorta to the pulmonary artery (this method was suggested and used by Keith Roberts in my department); later such a connexion can readily be disconnected, and the subclavian artery is available for use in setting up an extracorporeal circulation.

Machines Available

Many efficient machines are available. In spite of all criticisms the Gibbon–Mayo, the Melrose, and the Lillehei–de Wall systems can deliver adequate quantities of fully oxygenated blood to the patient with the heart and lung inflows and outflows cut off; haemolysis and defibrination are no longer problems, and metabolic acidosis in the patients will not develop if the use of the artificial circulation is scrupulously correct in all details. With the additional help of cardiac arrest produced by potassium citrate (Melrose), operations of up to 40 minutes and over can be carried out deliberately on a heart which, by reason of its arrest, has no need for metabolic changes; it behaves just as a limb does when its circulation is arrested by a tourniquet.

The startling advance made in several American clinics in the use of extracorporeal circulation should make us inquire into our own apparent slowness. I believe purely individual attempts to do this work will fail; not only is an adequate team required, but the work must be done in a reasonably sized department where the team engaged in the research work will be the one to perform in the operating theatre.

It is, I believe, the human factor that is now the important one and not the machines. Believing this, we decided, after seeing all the machines in action, that with our own limited resources the Lillehei–de Wall system would be the most suitable. Our immediate objective was to do our first work with the one object of getting dogs to survive from the outset, and, by spending a few months in the preliminary setting up of the apparatus, we have succeeded in achieving this. This small achievement (largely due to the efforts of my senior registrar, L. D. Abrams) is mentioned only because I think that in many clinics too many fresh ideas are being used before the experimenters have mastered the details of team-work. I only wish I could present results in patients.

The correct driving of the machine and the interpretation of the necessary monitoring (the electroencephalograph to tell us of the state of cerebral oxygenation, the recording of venous and arterial pressures, the exact knowledge of the total circulating fluid in the patient, and the *p*H of the blood) are essential.

Kirklin, Patrick, and Theye (1957) have described succinctly and clearly the requirements that must be fulfilled: "The maintenance of life by whole-body perfusion for one hour, during which time open cardiac operation is performed, can be accomplished at a very low risk provided all details are properly managed. While sporadically satisfactory results can be obtained otherwise, uniformly excellent results demand a thorough knowledge of the myriad of factors affecting the adequacy of the procedure, a carefully trained team, and proper equipment."

It is not over-caution which makes me say that it is easy to proffer a multitude of excuses for failure and defeatist views about the biological defects of the system in use. In the laboratory we have found that criticism which says that the blood volumes cannot be checked, that bleeding with the use of heparin is severe, that haemolysis is bound to occur and fibrinogen to be lost, and that acidosis is inevitable is readily rebutted. Refuting the theoretical objections to the bubble oxygenator and its modifications, it can be stated that blood can be kept fully oxygenated and carbon dioxide adequately eliminated, and that human blood when put through the oxygenator behaves always according to the classical pattern of the dissociation curve.

The problem of open cardiac surgery is by no means solved once the artificial circulation is in motion: the anatomical defects seen at open cardiotomy are so different from the diagrammatic representations or post-mortem appearances. The careful studies of Brock (1957) on pulmonary stenosis and the excellent descriptions of ventricular septal defects by Kirklin, Harshbarger, Donald, and Edwards (1957) and Lillehei *et al.* (1957) are essential reading for any surgeon who even contemplates the repair of these malformations. The surgeon has returned to claim part of his heritage of surgical anatomy; for, however careful the study is in the post-mortem room or in the radiological department, the pathological anatomy of the living can shatter disconcertingly the armchair conception of the abnormality. Having seen such masters as Kirklin and Lillehei, I do not feel, however simple they made it appear, that this surgery will be easy for many a day.

Conclusion

I have attempted a brief summary of the progress in cardiac surgery in the last ten years. I have for reasons of time omitted much; the surgery of valvular incompetence and of cardiac ischaemia has not been discussed, as I believe the real advances in these fields have still to come, though much has been done. The treatment of cardiac tumours and cysts and of aneurysms of the great thoracic vessels is in itself a large field in which spectacular achievements have been made. I wish I could offer the real summit of this progress, the complete correction of the tetralogy of Fallot: my account breaks off at this exciting stage. As I disentangle myself from the coils of the cardiac catheter, the magic of the electrocardiograph, and the complexities of the circulation I know I am guilty of having avoided many issues. I take comfort in the words of my favourite essayist to his friend Coleridge, "Cultivate simplicity."

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CHLOROTHIAZIDE IN CONTROL OF ASCITES IN HEPATIC CIRRHOSIS

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Ascites in cirrhosis of the liver is associated with a raised portal venous pressure and a lowered serum albumin level. Sodium is retained in the body as ascites accumulates, and urinary sodium is extremely low, most of the dietary intake passing into the peritoneal cavity. The urinary sodium/potassium ratio is reduced; this probably reflects the effects of aldosterone, increased amounts of which may be found in the urine of some cirrhotics with ascites (Wolff *et al.*, 1956). Ascites can often be controlled by rigid restriction of sodium intake and the use of diuretics (Eisenmenger, 1952; Atkinson *et al.*, 1954). The organic mercurials have been consistently useful, their only drawback being the necessity for parenteral administration; toxic effects are rare. An equally powerful but oral diuretic with no toxic properties would be of great value.

The new oral diuretic, chlorothiazide (6-chloro-7-sulphamyl-1-1,2,4-benzothiadiazine-1,1-dioxide; "saluric," "chlotride," "diuril") has been successfully used in patients with chronic cardiac failure (Moyer *et al.*, 1957; Bayliss *et al.*, 1958; Slater and Nabarro, 1958), and this prompted us to give it to patients with cirrhosis complicated by ascites. Chlorothiazide is chemically an aromatic sulphonamide derivative. Experimentally, in dogs, intravenous administration results in increased sodium and potassium excretion (Ford *et al.*, 1957). Its primary action, like that of the mercurial diuretics, seems to be potent inhibition of tubular reabsorption of sodium with no significant effect on renal blood flow or glomerular filtration rate. The increased excretion of sodium is balanced partly by increased chloride loss and also by an increased bicarbonate excretion. This anion excretion pattern is reminiscent of the carbonic anhydrase inhibitors such as acetazolamide ("diamox"), and chlorothiazide *in vitro* is a potent inhibitor of carbonic anhydrase. Unlike acetazolamide, however, its action does not depend only on bicarbonate excretion, and renal loss of bicarbonate is not profound enough to cause a metabolic acidosis and so inhibit further diuretic action by limiting the availability of the bicarbonate ion.

Patients Studied and Methods

Chlorothiazide was given orally in a dose of 2 g. a day (0.5 g. six-hourly) in 15 courses to 13 patients with Laennec's (portal or post-necrotic) cirrhosis complicated by ascites and peripheral oedema (12 patients) or gross peripheral oedema alone (1 patient) (Table I). A history of the neuropsychiatric complications of liver disease (confusion, flapping tremor, and disturbed consciousness) was obtained in seven instances. Four out-patients were also studied. The in-patients were investigated in a metabolic ward and received a sodium-

TABLE I.—*Cirrhotic Patients Treated with Chlorothiazide in Hospital*

Case No.	Age and Sex	Aetiological Factors	Duration of Ascites (Months)	Previous Treatment	Serum Bilirubin (mg./100 ml.)	Serum Albumin (g./100 ml.)	Past Hepatic Precoma or Coma
1	69 M	Alcoholism	18	Low Na diet. Mersalyl. Multiple paracentesis	0·5	2·7	–
2	38 M	Past hepatitis	36	Low Na diet. Mersalyl. Paracentesis × 3	1·1	3·3	–
3	50 M	—	5	Low Na diet. Mersalyl. Paracentesis ×10	0·8	2·2	–
4	53 F	—	14	Low Na diet. Mersalyl. Paracentesis ×25	0·4	3·1	–
5	50 F	—	3	Low Na diet. Mersalyl	2·5	2·5	–
6	39 M	Past hepatitis	3	Low Na diet. Mersalyl. Paracentesis ×2	4·0	2·7	+
7	47 F	Past hepatitis (porta-caval anastomosis)	12	Low Na diet. Mersalyl	1·2	2·4	+
8	50 F	—	6	Low Na diet. Mersalyl	2·1	2·2	+
9	65 F	—	15	Low Na diet. Mersalyl	1·2	3·1	+
10	47 M	Alcoholism	16	Low Na diet	0·4	2·3	+
11	66 F	Past hepatitis	1	Nil	2·6	2·5	+
12	10 F	—	1	Low Na diet	0·7	2·2	–
13	42 M	—	3	" " "	0·3	3·8	+

TABLE II.—*Effects of Chlorothiazide on Urine Volume, Electrolytes, and Body Weight*

Case No.	Before Chlorothiazide (Mean of 3 Days)				During Chlorothiazide (Mean of First 3 Days)				Duration of Treatment (Days)	Weight Loss (Kg.)	Diuretic Response	Complications
	Na	K	Cl	Vol. (ml./ 24 Hrs.)	Na	K	Cl	Vol. (ml./ 24 Hrs.)				
	mEq/24 Hours				mEq/24 Hours							
1	0·3	53	34	1,510	5·9	117	97	1,840	6	0	Poor	Hepatic precoma
2	0·5	27	2·9	1,175	53	62	90	1,410	6	0	"	
3	0·3	25	1·3	500	3·8	83	44	1,040	7	0	"	
4	0·5	25	1·2	920	5·9	67	60	1,410	6	0	"	
5	0·7	16	1·0	400	9	44*	18	430	7	0	"	
6 (1)	0·8	21	4·0	750	40	214*	163	1,640	2	4·4	Good	Hepatic coma
6 (2)	0·2	25	29	730	2·8	197*	172	990	6	0	Poor	
7 (1)	7	41	26	920	131	104	160	2,200	3	3·5	Good	Hepatic precoma. Epileptic fit
7 (2)	7	52	21	920	113	275*	225	2,200	5	3	"	Hepatic precoma
8	12	53	27	2,200	256	240*	342	4,300	7	6·1	"	
9	9	57	44	1,440	139	148*	206	2,700	7	2·3	"	
10	20	55	53	1,610	237	138	279	3,700	2	5·2	"	Hepatic coma
11	6·3	32	10	1,100	105	56	133	1,900	7	2·6	"	
12	8	60	16	2,100	66	112	74	3,600	4	2	"	E.E.G. slowing
13	11	62	23	2,060	73	123	160	2,530	6	2·8	"	Hepatic precoma

* Given potassium supplements.

restricted diet (22 mEq/24 hours) and approximately 70 mEq of potassium daily with a daily protein intake of 80 g.; one patient in impending hepatic coma (Case 11) could tolerate only 50 g. of protein daily.

The 24-hourly urine was measured and the sodium, potassium, and chloride content estimated, using standard and flame photometry techniques. Serum electrolyte levels were estimated so far as possible in the fasting state.

Electroencephalograms (E.E.G.s) were recorded serially. Slowing of the mean frequency was used as an indication of hepatic coma (Foley *et al.*, 1950; Parsons-Smith *et al.*, 1957; Laidlaw, 1958).

On six occasions oral potassium supplements in the form of potassium chloride in gelatin-coated capsules and/or potassium bicarbonate as an effervescent mixture were added (see Table V), and these were given routinely to the four out-patients. 1 g. of potassium chloride contains 13 mEq of potassium.

Results

On 9 of the 15 occasions the diuretic response to chlorothiazide was regarded as good (Table II). These patients showed a weight loss of at least 2 kg. and the urinary sodium output increased by more than 39 mEq. In the remaining six instances the response was poor, the weight showing no change, and, with one exception (Case 2), the urinary sodium output little or no increase. With one exception—Case 6 (1)—the patients who were refractory had a very low initial urinary sodium output (less than 1 mEq daily). This avid sodium retention with a low urinary sodium/potassium ratio indicates a profound degree of secondary hyperaldosteronism. Patients with a good diuresis showed a higher urinary sodium output and sodium/potassium ratio in the pre-treatment period, evidence of a less profound aldosterone effect.

In all patients chlorothiazide resulted in a twofold to threefold increase in urinary potassium output, and this was associated with a fall in serum potassium level in every patient not receiving potassium supplements (Table III). The increased urinary potassium and the drop in serum potassium level were most rapid and conspicuous in those having the greatest diuresis. The fall in serum potassium level was associated with the expected increase in the serum alkali reserve and a fall in serum chloride values (Table III).

TABLE III.—*Serum Electrolytes Before and Following Chlorothiazide, 2 g./day*

Case No.	Before Chlorothiazide				At Completion of Chlorothiazide				Duration (Days)
	Na	K	Cl	HCO_3	Na	K	Cl	HCO_3	
	mEq/l.				mEq/l.				
1	125	4·7	95	21·4	125	2·3	92	28·8	6
2	138	4·2	98	29	133	2·7	97	32	6
3	135	4·2	98	27	130	3·0	91	32	7
4	133	4·4	96	22	137	2·5	89	31	6
5	130	3·2	96	30	130	4·7*	98	25	7
6 (1)	128	4·5	102	20·7	127	2·4*	94·5	26·7	2
6 (2)	120	3·7	87	25	118	4·0*	87	22·2	6
7 (1)	133	4·0	106	21·8	137	2·9	99	26·4	3
7 (2)	138	3·9	103	26·1	133	3·1*	101	22·6	5
8	137	3·6	107	24	130	2·9*	104	25	7
9	135	4·5	105	27	138	3·7*	95	31·4	7
10	137	3·8	103	24·8	128	2·5	95	26·9	2
11	137	4·3	105	28	140	2·7	90	33	7
12	133	3·9	96	27	133	2·2	85	33·6	4
13	136	4·2	103	26	128	2·6	96	29	

* Potassium supplements given.

TABLE IV.—*Urinary pH and Bicarbonate Excretion on Chlorothiazide*

Case No.	Before Treatment (Mean of 3 Days)			During Chlorothiazide (Mean of First 3 Days)		
	Vol. (ml./24 hrs.)	*p*H	Bicarbonate (mEq/24 hrs.)	Vol. (ml./24 hrs.)	*p*H	Bicarbonate (mEq/24 hrs.)
13	2,060	6·9	6	2,530	7·1	26
1	1,510	5·9	3	1,840	6·8	23
14	900	6·5	2	800	6·8	5
15	1,020	6·4	3·2	2,030	6·9	21

Anions excreted consisted mainly of chloride, but there was a considerable deficit between the total urinary cations and the chloride output. In two control and two cirrhotic patients chlorothiazide resulted in a rise in urinary *p*H with a fivefold increase in bicarbonate excretion (Table IV). These results suggest that chlorothiazide was behaving not only as a choluretic (mercurial-like action) but also as a carbonic anhydrase inhibitor. The increase in bicarbonate and in potassium loss was reminiscent of the action of the carbonic anhydrase inhibitor acetazolamide.

Results obtained in a patient who proved refractory to chlorothiazide are shown in Fig. 1.

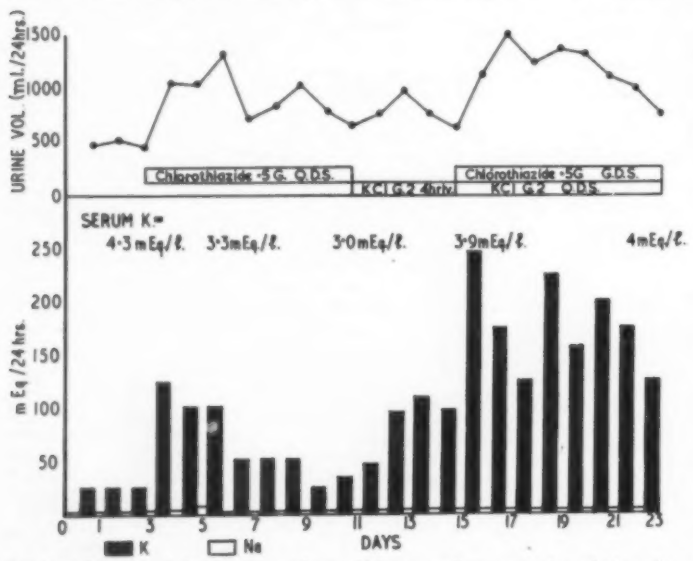

FIG. 1.—Case 3, cirrhosis and ascites. Urinary sodium excretion during the control period was less than 1 mEq daily and the Na/K ratio was low. Chlorothiazide increased the urinary sodium excretion to only 6 mEq/24 hours. The predominant cation lost was potassium, and as its excretion proceeded the serum potassium level fell. There was a small diuresis but insignificant weight loss. The addition of potassium supplements did not increase the urinary sodium excretion, but the serum potassium level did not fall.

Complications

Hypokalaemia, defined as a serum potassium below 3.5 mEq/l., was noted in all nine patients receiving chlorothiazide without potassium supplements. This state, although sometimes symptomless, is potentially dangerous. In six cases studied the changes of potassium deficiency developed in the electrocardiogram, and in two of these cases ventricular extrasystoles were a further manifestation of hypokalaemia.

Potassium supplements (78–250 mEq/24 hours) were given six times (Table V). On four occasions this proved insufficient to balance the urinary loss, and serum potassium values fell. The other two patients showed a poor diuretic response to the drug; urinary potassium loss was balanced by the extra potassium, and hypokalaemia was not seen.

TABLE V.—*Effect of Potassium Supplements.*

Case No.	Duration of Treatment (Days)	K supplements (mEq/24 hrs.)	Before Chlorothiazide		After Chlorothiazide		Diuretic Response
			Serum K mEq/l.	Urinary K (mEq/24 hrs.) (3-day Mean)	Serum K (mEq/l.)	Urinary K (mEq/24 hrs.) (3-day Mean)	
5	7	78	3·2	16	4·7	44	Poor
6 (1)	2	100	4·5	21	2·4	214	Good
6 (2)	6	256	3·7	25	4·0	197	Poor
7 (2)	5	256	4·0	52	3·1	275	Good
8	7	256	3·6	53	2·9	240	"
9	7	78	4·5	57	3·7	148	"

Hepatic Precoma and Coma

This syndrome was noted in 7 of the 13 in-patients treated (Table II). It was usually associated with a good and rapid diuretic response to the chlorothiazide. Two patients passed into deep coma after only two days' therapy.

Case 10.—A man of 47, an alcoholic with cirrhosis, was admitted to hospital for assessment for porta-caval anastomosis following haemorrhage from oesophageal varices. Examination revealed hepatosplenomegaly and moderate ascites with ankle oedema. Slight hepatic fetor and "flapping" tremor disappeared within a few days of admission to hospital. Neuropsychiatric complications had not followed the haemorrhage, but there was a history of previous hepatic precoma. Chlorothiazide resulted in a massive diuresis, 5 kg. in weight being lost in two days. However, within 24 hours of commencing the drug the fetor and tremor returned and the E.E.G. showed slowing. The next day he became violent, requiring considerable restraint, and passed into deep coma, regaining consciousness only after 36 hours.

Case 6 (1).—This patient with cirrhosis and a past history of hepatitis had considerable ascites. He responded to chlorothiazide with a good diuresis, but soon exhibited hepatic fetor, tremor, and confusion, and passed into coma. A further course of chlorothiazide given later in his illness—Case 6 (2) in Table II—when he had developed even greater retention of sodium with a fall in his serum sodium level, was not accompanied by a diuresis, and neither was there any neuropsychiatric electroencephalographic deterioration.

Three other patients exhibited the features of hepatic precoma while receiving chlorothiazide, and in one of these there was an associated major epileptic fit. A further patient developed only gross slowing of the E.E.G., and the chlorothiazide was then stopped. The E.E.G. proved the most sensitive record of impending neuropsychiatric disturbance, but major electrical abnormalities were always accompanied by clinical evidence of hepatic precoma.

Only one patient (Case 11) developed hepatic coma without a coincident gross diuresis. This complication was noted six days after beginning the drug.

Two patients—Cases 6 (1) and 7 (2)—developing neuropsychiatric changes were receiving supplements of 100 and 256 mEq of potassium daily (Table V). Supplements were also given on four other occasions and to four out-patients, and the changes of hepatic precoma were not seen.

Continued Treatment in Out-patient Department

Four cirrhotic patients with ascites were previously well stabilized as out-patients on a low-sodium diet and mersalyl twice weekly. Chlorothiazide (2 g. daily) was substituted for the mercurial and was given continuously for two to three days in the week. All the patients received 3 to 6 g. of potassium chloride daily in capsules. Two responded well, the ascites being controlled or regressing; and two showed a poor response, the ascites increasing (Table VI). One of those who became refractory to chlorothiazide after four weeks had been followed previously for four years and had continuously responded to mersalyl. She was very disappointed to return to the injection treatment, for it had caused her considerable diarrhoea.

There was a tendency to develop hypokalaemia when chlorothiazide was given on more than two days in the week and when potassium supplements were less than 78 mEq daily (6 g. of KCl). Neurological complications were not seen, the serum potassium not reaching as low levels as in the patients on continuous therapy.

TABLE VI.—*Results of Chlorothiazide Therapy in Four Cirrhotic Out-patients with Ascites. The Drug was Given Continuously for Two to Three Days Weekly. No Neurological Complications were Seen*

Case No.	Duration of Treatment (Weeks)	K Supplements (mEq/24 Hours)	Serum K (mEq/l.)		Result
			Before	After	
14	4	39	4·1	3·3	Slow gain of 3 kg.
8	4	39	3·6	2·9	" " " 2 "
15	4	39	4·5	3·7	Good. Lost 2 kg.
7	2	78	4·4	4·7	Good. Weight constant

Comparison of Chlorothiazide with Mersalyl

In five patients the sodium and potassium excreted after 0.5 g. of chlorothiazide six-hourly for four doses was compared with that following 2 ml. of mersalyl intramuscularly (Fig. 2). On three occasions mersalyl therapy preceded

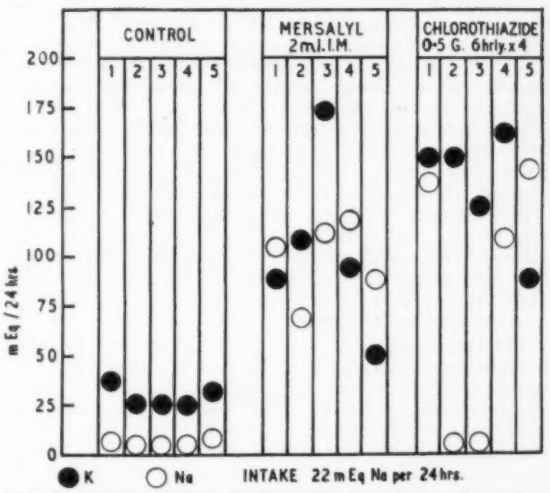

FIG. 2.—Cation excretion in five cirrhotic patients with ascites before and after chlorothiazide or mersalyl.

chlorothiazide and on two occasions the regime was reversed. In all five patients mersalyl increased the sodium excretion, an effect that was noted in only three patients after chlorothiazide. Potassium excretion after mersalyl was lower than the sodium loss in three patients. With chlorothiazide the reverse situation was noted, with a 24-hourly loss of sodium exceeding that of potassium in only one case. All these patients showed a very low initial sodium excretion in the urine. Chlorothiazide seemed less able than mersalyl to promote sodium excretion in such patients, but potassium loss was greater.

Discussion

Chlorothiazide has had only limited clinical trials in patients with ascites and cirrhosis. In a series of nine cirrhotic patients Laragh *et al.* (1957) found a good diuresis in three, a partial response in three, and no effect in three. Other authors have described only one or two cases, and the results are variable. In our patients the response was proportional to the severity of the fluid retention, and those with very low initial urinary sodium outputs showed little or no diuresis. These patients were by no means in a "terminal state" (Hecker and Sherlock, 1956), and the majority responded well to a mercurial diuretic. Patients with less avid sodium retention often showed a dramatic diuresis after chlorothiazide. All these in-patients were receiving a strict low-sodium diet. Out-patients cannot usually achieve such a regime, and here chlorothiazide may be useful, although two such patients became refractory to

the drug after a few weeks' treatment. In such instances alternation with mercurial diuretics may be valuable. Chlorothiazide is convenient to use and patients prefer it to mercurials. The cost, however, must be remembered, for 2 g. of chlorothiazide for three days costs 7s. 6d., in contrast to 2 ml. of mersalyl, which costs 2d.

Hypokalaemia has been well recognized as a complication of chlorothiazide treatment of congestive heart failure (Bayliss *et al.*, 1958) and has also been reported in cirrhotic patients (Laragh *et al.*, 1957; Richards, 1957; Schreiner and Bloomer, 1957; Slater and Nabarro, 1958). It was a consistent finding when our patients had a good diuresis. Hypokalaemia can be partly controlled by potassium supplements, and 3 g. of potassium chloride daily should be given to all patients receiving the drug. In some instances, however, the potassium loss far exceeds this amount and with continued therapy hypokalaemia becomes inevitable. The potassium supplements can be increased to 6 g. of potassium chloride daily, but the patient may not tolerate even this amount of an essentially nauseating substance.

The large number of patients developing impending or actual hepatic coma was unexpected, although single instances have been reported by Richards (1957) and Castro (1957). The high incidence of a past history of hepatic coma in our patients (7 out of 13) was not more than is usually encountered in cirrhotic patients with ascites. Fluid retention can be regarded as a bad prognostic sign, and other signs of liver failure such as jaundice or neuropsychiatric complications are therefore common. Precoma of minor degree can easily be overlooked if the possibility is not considered. Abnormal electroencephalographic recordings are even more frequent. This distinction of patients with a past history of precoma was of practical importance, for no patient treated with chlorothiazide developed these complications unless there was this tendency. The drug should be given extremely cautiously if such a history is elicited or if neuropsychiatric abnormalities can be detected.

The mechanism of the hepatic coma is uncertain and will be discussed more fully later (Read *et al.*, 1958). It could not be related to failure of the diseased liver to metabolize chlorothiazide, for blood levels in cirrhotic patients did not differ from those obtained in normal subjects after a similar loading dose. Chlorothiazide *in vitro* has carbonic anhydrase inhibitor properties (Beyer *et al.*, 1957), and this is confirmed by the finding of an increased urinary excretion of bicarbonate and an accompanying rise in urinary *p*H after its administration. The carbonic anhydrase inhibitor acetazolamide induces hepatic precoma in some patients with liver disease (Webster and Davidson, 1956), and this has been related to a blockage in uptake of ammonium by peripheral tissues (Dawson *et al.*, 1957). Chlorothiazide might act in a similar way, although perhaps with less potency. Episodes of hepatic coma and precoma associated with chlorothiazide therapy have usually been accompanied by an elevation of the fasting arterial ammonium level (Read *et al.*, 1958). It seems unlikely that this is the only way in which chlorothiazide is toxic, for the effects are not proportional to the dose, and in some instances recovery may ensue when potassium is given.

A correlation was noted between the extent of the diuresis and the development of precoma. Patients with cirrhosis and ascites may develop hepatic precoma after abdominal paracentesis, and, although the mechanism is not clear, alterations of osmolarity and loss of electrolytes must be considered. A diuresis of comparable amount may act similarly. Potassium loss may be of particular importance (Read *et al.*, 1958). The potassium deficit associated with neuropsychiatric complications in cirrhotic patients is of the order of 300 mEq. This is a relatively small amount, but the brain of a patient who has experienced hepatic precoma may be particularly sensitive to many metabolic insults, of which hypokalaemia may be one (Sherlock, 1958). It is unfortunate that therapy is particularly dangerous in the group having the most satisfactory diuresis.

Summary

Chlorothiazide, 2 g. daily, was administered on 15 occasions to 13 patients with cirrhosis of the liver and ascites. On nine occasions the diuretic response was regarded as good; in the remaining six instances the response was poor. Refractory patients had an initial urinary sodium output of less than 1 mEq daily. Two refractory patients to chlorothiazide responded well to mersalyl.

Urinary potassium output increased and all patients not receiving potassium supplements developed hypokalaemia. Impending or actual hepatic coma was noted in 7 of the 13 patients treated. It was usually associated with a good diuretic response to chlorothiazide and in those with a previous history of hepatic precoma. The possible mechanisms of this reaction to chlorothiazide are discussed.

Four out-patients were treated for longer periods with intermittent chlorothiazide and continuous potassium supplements. Neuropsychiatric changes were not seen, but two patients became refractory to the drug.

Continuous chlorothiazide therapy should not be given to cirrhotic patients outside hospital. Potassium chloride (3–6 g. daily) should be given to all patients with cirrhosis receiving the drug. Particular care should be taken in patients with a previous history of the neuropsychiatric complications of liver disease.

We wish to thank Merck, Sharp and Dohme Ltd. for generous gifts of chlorothiazide ("saluric"), Miss Janet McLaren, B.Sc., for biochemical assistance, and Miss A. M. Lees for taking the electroencephalograms. We are also indebted to the Medical Research Council for a personal grant to one of us (J.L.) and for help with expenses.

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At a meeting of the Huntingdon Rural District Council on March 28 the council said farewell to Dr. J. R. GARROOD, who had been their part-time medical officer of health for 34 years. He took office on the death of his father-in-law, Dr. L. Newton, who was appointed as the council's first M.O.H. in 1894. Dr. Garrood was 84 when he retired.

EARLY OBSERVATIONS ON THE DIURETIC EFFECT OF ORAL CHLOROTHIAZIDE

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It is well known that digitalis and mercurial diuretics are the two most potent agents in the treatment of heart failure, and that mercurial compounds are particularly useful if the heart rhythm is regular. Up to the present time oral diuretics have compared unfavourably with parenteral therapy in increasing urinary output and lessening pulmonary congestion, especially when heart failure is severe. Aminometradine (" mictine ") is less potent than mersalyl; its maximum effect is often delayed, and treatment may have to be limited because of gastro-intestinal intolerance (Platts and Hanley, 1956). Acetazolamide (" diamox ") compares unfavourably with mersalyl, and it is doubtful if it serves any useful purpose in the treatment of patients with severe congestive heart failure (Relman *et al.*, 1954). Jose and Wood (1958) compared the diuretic action of mersalyl and amisometradine (" rolictou ") in 20 patients and found the oral diuretic to be less than half as potent. It is clear, therefore, that, should an oral diuretic become available that is equal to or better than the well-established drugs given intramuscularly, it would be of great use in therapeutics and of immense practical value. From our preliminary observations we believe that chlorothiazide (" saluric," " chlotride," " diuril ") may well prove to be such a drug.

Chlorothiazide was first synthesized by Novello and Sprague (1957) and is designated chemically as 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide. It produces water diuresis in man by promoting the excretion of sodium and chloride in equimolar amounts. Its diuretic action is therefore similar to that of mercurial compounds.

The main objects of this paper are to record our early observations on the potency of chlorothiazide in water diuresis and to compare its efficacy with parenteral mercurial diuretics.

Methods

The effect of oral chlorothiazide on the urinary output was observed in 20 in-patients, all with clinical oedema or pulmonary congestion from heart failure. Seventeen were also given parenteral mercaptomerin (" thiomerin ") or mersalyl. All the patients were confined to bed during the period of investigation and their ventricular rate was kept constant with or without digitalis. The 24-hour fluid intake and urinary output were recorded in fluid ounces. The fluid intake was inconstant, 30–50 oz. (852–1,420 ml.) in one day, and the sodium intake calculated as sodium did not exceed 0.7 g. daily.

We were aware of the spontaneous diuresis which may occur when a patient is first rested in bed, and that the initial diuresis in any patient with heart failure is usually better than the response obtained by later therapy. We therefore deliberately chose to use parenteral diuretics first in 16 cases. In 10 patients several injections were given initially, and so the oral effect of subsequent chlorothiazide was thought to be of greater significance. In six patients mercurials were used only once or twice before instituting oral therapy. The dosage of mersalyl or mercaptomerin used was 2 ml. intramuscularly at varying intervals without preceding ammonium chloride. Chlorothiazide, 1 g., was given twice a day, at 10 a.m. and 2 p.m., for four consecutive days, followed by an interval of three to four days before a further course was started.

The diuresis was compared in units of two days. The mercurial diuretic was given on the first day only, and chlorothiazide was administered on each of the two days under consideration. In practice, parenteral diuretics are rarely given on consecutive days, whereas chlorothiazide may be so given. Evans and Paxon (1941) defined the diuretic index as " the excess of the daily output of urine over the fluid intake, both measured in ounces." We have used this as a basis in our study, but recorded the total diuretic index for two successive days because the mercurials often continue to be effective on the day following the injection. The serum electrolytes were estimated before and after treatment in 13 cases.

Results

The average diuretic index for every case was calculated from the number of two-day periods of treatment, and is recorded in Table I. The total number of two-day periods of treatment is shown in each case—for example, Case 1 received eight two-day periods of therapy with mercurial diuretics and six and a half two-day periods (that is, 13 days) on chlorothiazide. In 16 of the 20 patients mercurial diuretics were given first. In the remaining four chlorothiazide was given initially for various reasons. Two patients (Cases 7 and 8) had been given mercurials at weekly intervals for over a year without clinical improvement, and this was the prime reason for their admission to hospital. One patient (Case 4) was inadvertently given the oral diuretic initially, and the diuresis and clinical improvement was such that she subsequently refused parenteral therapy. Prior to admission Case 3 developed a rash after mercaptomerin and it was therefore considered wise to start with the oral diuretic. Later it was found that mersalyl caused no such skin reaction.

Of the 17 patients given both forms of diuretic therapy, Case 11 showed the most satisfactory response to chloro-

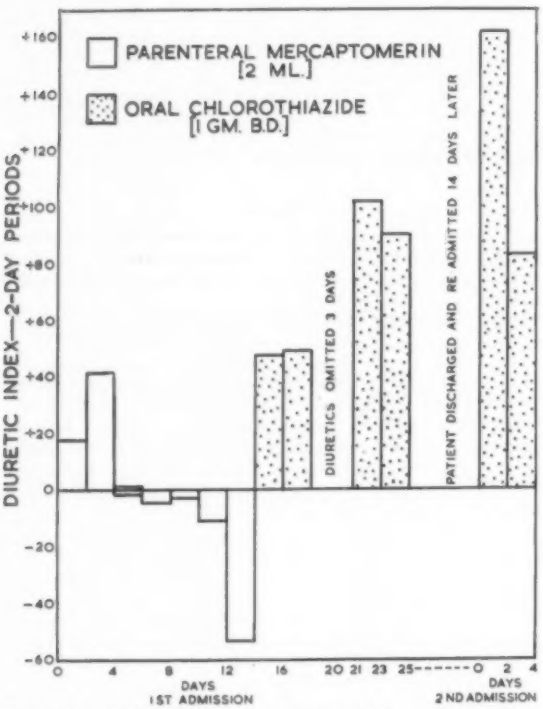
TABLE I.—*Average Diuretic Index (Per Two-day Period) in 20 Patients, Following Mercurial Diuretics and Chlorothiazide*

Case No.	Age and Sex	Cause of Heart Failure	Parenteral Mercurials (2 ml. on 1st Day of Each 2-day Period)		Oral Chlorothiazide (1 g. b.d. on Both Days of Each 2-day Period)	
			No. of 2-day Periods	Average Diuretic Index	No. of 2-day Periods	Average Diuretic Index
1	58 F	R.H.D.	8	−18	6½	+42
2	68 F	C.A.D.	12	+10	10	+19
3*	65 M	C.A.D.	4	+12	3	+20
4	67 F	P.H.D.			3	+51
5	51 F	R.H.D.	23	+3	6½	+10
6	74 M	H.H.D.	19	+20	5½	+55
7	60 M	C.A.D., H.H.D.			6	+75
8	62 F	R.H.D.			2	+53
9	53 M	H.H.D.	1	+56	3½	+93
10	65 F	C.A.D.	1	+62	4	+45
11	59 F	R.H.D.	7	0	4	+72
11 (a)	59 F	R.H.D.			2	+124
12	54 M	P.H.D.	15	+22	4	+13
13	60 F	P.H.D.	6	−8	4	+14
14	62 M	C.A.D.	5	+10	2	+16
15	64 M	P.H.D.	3	+35	3	+29
16	67 M	R.H.D.	2	+68	4	+53
17	60 M	C.A.D.	2	+41	4	+28
18	68 M	C.A.D.	2	+24	5	+39
19	74 M	C.A.D., H.H.D.	2	+30	6	+28
20	58 M	R.H.D.	5	+49	4½	+66

C.A.D. = Coronary artery disease. H.H.D. = Hypertensive heart disease. P.H.D. = Pulmonary heart disease. R.H.D. = Rheumatic heart disease.
* Patient given mercurials after chlorothiazide.

thiazide, and this is illustrated in the Chart. During her first admission she had a higher average diuretic index following chlorothiazide (+72) than mercaptomerin (0), although the latter was given first in seven two-day periods. When readmitted she was given chlorothiazide initially for four successive days with an average diuretic index of +124.

It can be seen (Table I) that where mercurial diuretics were not given in hospital the average diuretic index on chlorothiazide was highly satisfactory in all three patients (Cases 4, 7, and 8). In the remaining 17 patients both types of diuretic agent were used and the average diuretic index was superior following chlorothiazide in 11. Mercurial diuretics were apparently superior in six patients (Cases 10,


PARENTERAL MERCAPTOMERIN [2 ML.]
ORAL CHLOROTHIAZIDE [1 GM. B.D.]
DIURETIC INDEX—2-DAY PERIODS
DIURETICS OMITTED 3 DAYS
PATIENT DISCHARGED AND RE ADMITTED 14 DAYS LATER
DAYS 1ST ADMISSION
DAYS 2ND ADMISSION

Case 11. Action of initial mercaptomerin, seven two-day periods, compared with subsequent chlorothiazide, six two-day periods, shown by diuretic indices over two-day periods.

12, 15, 16, 17, and 19). It is clear that this could be attributable in five (Cases 10, 15, 16, 17, and 19) to the use of only one to three preliminary injections when considerable fluid retention was present. In Case 12 it would seem that the mercurial compound was superior, but when chlorothiazide treatment was started his clinical oedema had almost disappeared.

Six patients (Cases 9, 10, 16, 17, 18, and 19) were given only one or two mercurial injections initially, followed by chlorothiazide. We calculated the average of the diuretic indices obtained from all six patients following each form of therapy, and the findings are shown in Table II.

It was expected that this analysis would favour mercurial diuretics because of the satisfactory diuretic response usually obtained in early therapy. Actually the average diuretic

TABLE II.—*Average Diuretic Index of Six Patients Given One or Two Mercurial Injections Initially*

No. of Cases	Mercurials (10 × 2-day Periods)		Chlorothiazide (26½ × 2-day Periods)	
	Sum of Average Diuretic Indices	Average	Sum of Average Diuretic Indices	Average
6	281	+47	286	+48

indices obtained were almost identical. It is appreciated that the variability of diuresis obtained in these cases individually was such that in a larger series the average indices might not have been so similar.

In only five patients was chlorothiazide given initially, and included among these was the one patient (Case 11a) who was given chlorothiazide only on her second admission. The average of the diuretic indices of these five patients is shown in Table III. The average diuretic index is high

TABLE III.—*Average Diuretic Index of Five Patients Given Chlorothiazide Initially*

Chlorothiazide (16 × 2-day Periods)		
No. of Cases	Sum of Average Diuretic Indices	Average
5	323	+65

(+65). Only one of these patients received subsequent mercurials, and so a comparison of the diuretic agents cannot be made in these five cases. A relevant comparison can be made with the average diuretic index obtained following mercurials in those cases which were given only one or two injections initially, as shown in Table II (+47).

The average of the indices of 10 patients who were given more than two mercurial injections initially is shown in Table IV. It will be noted that the average index proved

TABLE IV.—*Average Diuretic Index of 10 Patients Given More than Two Mercurial Injections Initially*

No. of Cases	Mercurials (103 × 2-day Periods)		Chlorothiazide (50 × 2-day Periods)	
	Sum of Average Diuretic Indices	Average	Sum of Average Diuretic Indices	Average
10	123	+12	336	+34

to be higher in the chlorothiazide group. Some of these cases were showing a diminishing response to mercurials and may have been developing drug tolerance, but the subsequent effect of chlorothiazide was gratifying, as shown particularly in Cases 6 and 11 (Table I).

The average of the indices in the whole series of 20 patients, including all courses of treatment, is given in Table V. This shows that the number of two-day periods was

TABLE V.—*Average Diuretic Index of all Patients*

Mercurials (117 × 2-day Periods)			Chlorothiazide (92½ × 2-day Periods)		
No. of Cases	Sum of Average Diuretic Indices	Average	No. of Cases	Sum of Average Diuretic Indices	Average
17	416	+24	20	945	+47

approximately the same in both groups, and that the average diuretic index of 20 patients was higher in the chlorothiazide series (+47) than that of 17 patients treated with mercurial diuretics (+24). As a result of combined therapy the signs of pulmonary congestion and peripheral oedema disappeared in all our 20 patients.

The serum electrolytes were determined in 13 patients, and in these the serum sodium and chloride were not significantly altered. The serum potassium did not fall to below 3.3 mEq/l. in any of these patients. In five it fell to between 3.3 and 3.9 mEq/l. Symptoms of hypokalaemia did not develop in these.

Discussion

We are conscious of the inherent difficulties in a comparison of diuretic agents because of the many variables that are introduced into any such study. We have already mentioned the spontaneous diuresis that may occur in a patient following bed rest alone, with or without digitalis, and the advantage possessed by the initial diuretic agent. Obviously, it is difficult to assess the degree of fluid retention in any

patient at a given time, and the diuretic response to any drug must be influenced by this clinical state. In 16 of our patients any likely advantage in diuretic action was given to mercurials as they were given before chlorothiazide. It is evident from our results that a significant diuresis was obtained with subsequent chlorothiazide, and our preliminary observations suggest that this drug is at least as potent as parenteral mercurials, or more so. In the patients who were given chlorothiazide initially the diuretic response was excellent. Our study of this small series of patients has convinced us that chlorothiazide is the most potent oral diuretic now available. If subsequent trials confirm our findings we will have an efficient diuretic which has the merits of practicability and ease of administration. Our patients were grateful that a change had been made from repeated injections, particularly as most of them noticed that the effect was usually better. The practical advantage of the oral method in domiciliary practice is obvious. Toxic manifestations did not appear in a single case, and, in particular, no gastrointestinal disturbances occurred.

The most important side-effect of oral chlorothiazide is hypokalaemia (Bayliss *et al.*, 1958; Slater and Nabarro, 1958). In the dosage used by us the serum electrolyte levels were not markedly affected, but it is known that if continuous daily therapy is instituted hypokalaemia occurs. Further work on the electrolyte changes following prolonged treatment is necessary, as this would seem to be the only serious disadvantage to the use of chlorothiazide in general practice. None of our cases was given supplementary potassium, but it must be stressed that the dose of chlorothiazide never exceeded 2 g. in one day, and that it was never given for more than four consecutive days at intervals of three to four days. Only one patient received as much as 20 days of intermittent therapy. We do not therefore wish to imply that supplementary potassium is unnecessary during treatment with chlorothiazide, but it is possible that this can be avoided if its administration is interrupted by free periods according to the procedure we adopted.

Summary

Oral chlorothiazide was given in doses of 1 g. twice daily to 20 patients with heart failure. In 17 of these 2 ml. of a mercurial diuretic was given parenterally and in 16 it was given initially. To compare the value of these diuretic agents varying courses of intermittent therapy were used. The response obtained was measured as the diuretic index over a two-day period.

Chlorothiazide produced a good therapeutic effect in all cases, and our results suggest that it is as effective as the parenteral diuretics, or more so.

In the short and intermittent courses of treatment which we used only a slight fall in serum potassium was recorded in five patients. Toxic effects were not observed in any of our patients.

We are grateful to Messrs. Merck, Sharp and Dohme Ltd. for supplies of chlorothiazide (" saluric ").

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Endemic Goitre, a select bibliography on world distribution, has been published by the Chilean Iodine Educational Bureau (Chile House, Ropemaker Street, London, E.C.2). It contains over 1,000 references to the literature of the last 150 years, arranged on a geographical basis. There are also author and country indexes.

TREATMENT OF HAY-FEVER WITH LOCAL HYDROCORTISONE HEMISUCCINATE SODIUM

BY

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During recent years various analogues of hydrocortisone have been used by local application to the nasal mucosa in the treatment of hay-fever. Owing to the relative insolubility of the free alcohol and acetate derivatives, previous workers have used these substances either incorporated in a snuff or as nose-drops in weak concentration. Pennypacker (1954) used nose-drops containing the free alcohol of hydrocortisone dissolved in saline in a strength of 0.2 mg. per ml., which represents its maximum aqueous solubility; vasoconstrictors were also included. Herxheimer and McAllen (1956) employed hydrocortisone acetate dispersed in lactose and used as a snuff, the maximum daily dose being 15 mg. Godfrey *et al.* (1957) also used a snuff, but one containing prednisolone in a maximum daily dose of 2 mg.

The development of compounds of hydrocortisone which are highly soluble in water has introduced a new factor into its use as a local therapy. Such compounds are likely to enter the tissues more rapidly and in higher concentration than the less soluble ones. Any beneficial actions of hydrocortisone in its less soluble forms might be expected to occur with greater speed and lower total dosage with these new preparations. In the present study we describe the use of a highly soluble preparation used in nose-drops. This was hydrocortisone hemisuccinate sodium, which has appeared to be effective when used locally in ulcerative colitis, as described in a previous article (Truelove, 1957), in which is also included a brief review of its properties.

Procedure

Hydrocortisone hemisuccinate sodium suffers from a minor disadvantage for use in nose-drops in that it undergoes in aqueous solution a slow hydrolysis with the liberation of hydrocortisone itself, which is liable to precipitation because of its low solubility. The rate of hydrolysis is dependent upon the intensity of light, and the process can be slowed by keeping the solution in a dark glass bottle. Under these conditions the solution is reasonably stable for 48 hours.

The hemisuccinate was therefore supplied by Glaxo Laboratories in the form of tablets. Each tablet contained the equivalent of 2.5 mg. of free hydrocortisone. The nose-drops were prepared each day by the patient dissolving one or more, as ordered, of these tablets in 5 ml. of normal saline contained in a small dark glass bottle fitted with a nasal dropper. Each patient began by using two tablets to the bottle, yielding a concentration of 1 mg. of hydrocortisone per ml. Some patients who responded well to this initial concentration continued their treatment with one tablet in the bottle. Others, in whom the initial concentration was ineffective, used a higher concentration.

The patients began treatment by applying three drops in each nostril four times a day. The nasal droppers yield 1-minim (0.06-ml.) drops—that is, 15 drops per ml.—so that the patients received 2 ml. or less of the solution daily. In

other words, the initial treatment involved the daily use of 2 mg. or less of hydrocortisone.

Patients were instructed to apply the nose-drops while lying supine with the head hanging down in a fully extended position, which was to be sustained for a minute or so, during which time gentle sniffing was practised to disperse the solution throughout the nose.

Selection of Patients

The 22 patients who were treated all had a history of attacks of hay-fever occurring regularly during the grass-pollen season. They were all suffering from marked symptoms of hay-fever, present at least for several days, when treatment was begun.

Some of them had had pre-seasonal pollen injections in previous seasons. Of these, some had never derived benefit from these injections, while others had had some benefit but had not continued with the treatment. Six received injections before the present season, but the onset of hay-fever seemed to indicate that these had been ineffective. The group as a whole is unrepresentative of hay-fever patients in general, as it contained an unduly high proportion who were not responsive to prophylactic pollen injections.

The ages of the patients varied from 17 to 58 years. The length of history was also variable, ranging from 4 to 35 years.

Assessment of Therapy.—All patients were seen immediately before treatment was begun and a note was made of their symptoms. The nasal mucosa was inspected and smears were made from nasal swabs. It was not convenient to see patients daily, but they were generally seen at the end of approximately one week for further re-examination. Most of them were seen several times thereafter, and all of them at least once. From the point of assessing the symptomatic response it was a fortunate chance that the hay-fever season in 1957 coincided with an exceptionally long spell of dry, sunny weather lasting several weeks. For grass pollen the season lasted from early June until the second week in July.

Results

Eleven patients made a rapid improvement on the initial dosage of 1 mg. of hydrocortisone per ml. and became entirely symptom-free in the course of a period ranging from less than 24 hours to a few days. The response was never immediate. In other words, the agent did not behave like a vasoconstrictor. Even in patients who showed the most rapid return to normality the process was a steady one throughout. In those with a more gradual response, spread out over some days, the diminution of the symptoms followed a fairly constant pattern. All showed some improvement in the first 24 hours, with relief of nasal obstruction, although with spasmodic rhinorrhoea still occurring in provoking circumstances. Next followed a stage when the nose was easily irritated but the reaction was limited to a sneeze or two. This passed gradually into normality.

Of the 11 patients who did not respond favourably to the initial dosage, five were tried after a few days on double-strength drops (2 mg. per ml.). Of these, two made an excellent response, which was rapid in one and gradual in the other. The remaining three made no favourable response, and two of them experienced some nasal irritation from the drops.

At this time we inquired about the exact composition of the tablets and learned that the main excipient was sodium chloride, which we judged was acting as an irritant through its osmotic action when the higher doses were employed. It is only fair to add that the tablets were prepared for our use by the makers at high speed because we had decided to make this study only a very short time before the hay-fever season began. Preliminary trials were impossible and the tablets were used as soon as they were made. Nevertheless, the nature of the excipient is a matter of consequence, for we think it is possible that a considerable proportion of patients not responding to our initial dosage level would do so at higher dosages, which would still be very small in terms of any systemic action. We were precluded from any systematic exploration of this possibility during the present season by the osmotic properties of the tablets.

The subsequent course of those patients who responded well to the treatment is of interest in several connexions. The first is that the strength of the nose-drops could be reduced after a few days of normality without recurrence of symptoms. On the other hand, two patients who reduced the dose after only one day of normality promptly had a mild relapse but recovered immediately they returned to the original dosage.

Treatment was maintained for periods lasting from three to seven days after symptomatic normality was achieved and was then suspended. Some patients subsequently suffered a mild relapse in the course of the next few days, but in all cases this responded swiftly to one day's treatment, after which they were again symptom-free for at least several more days. A more pronounced stability of the nasal mucosa was displayed by three patients who had no nasal symptoms after the initial course of treatment. We regard this as a remarkable phenomenon because the hay-fever season was still in progress and symptoms were being experienced by the non-responders of the present series as well as by other patients in this area.

The fact that the patients who responded well to the original course of treatment were able to go through the remainder of the hay-fever season with little or no further use of the treatment was not due to absence of exposure to pollen. Some patients were heavily exposed because of their occupations or their pleasures. For example, one was a golf professional, another was a gardener, and a third, a student by avocation, spent many hours sailing on a river which runs through grassy meadows.

Eye Irritation.—The eye irritation so common in hay-fever was usually completely relieved *pari passu* with improvement in nasal symptoms. There were two exceptions in whom eye irritation continued to occur after protracted outdoor exposure, and these were driven to take an antihistamine for relief of this symptom; they claimed that this was more effective than when used before starting hydrocortisone treatment.

Chest Symptoms.—Five of the 13 patients who responded favourably to treatment had been accustomed to suffer from mild chest symptoms as a part of their hay-fever. In four of these patients the chest symptoms diminished as the nose improved. In three of these four, during the period of maintenance treatment, chest symptoms returned, in two taking a different pattern from the original one, in that nocturnal asthma occurred instead of morning cough and sputum. These secondary chest manifestations may have been related in some indirect way to the treatment, because they ceased when this was discontinued, the nose throughout remaining normal, even after treatment was stopped. The fifth patient suffered while on treatment from aggravation of an evening asthma which subsided a few days after stopping treatment. One other patient, not usually liable to chest symptoms, developed some cough during treatment.

Nasal Mucosa.—At the beginning of treatment, inspection of the nasal mucosa revealed it to be abnormal in all patients, although the type of change varied from patient to patient. In those who responded to treatment the mucosa was normal in appearance when they were symptom-free. In some who showed the gradual type of symptomatic response the appearance of the mucosa was normal at a stage when mild residual symptoms, such as irritability, were still present. In general, the non-responders showed no change in the mucosa.

Nasal Smears.—Examination of the nasal smears has not been helpful. The appearances during the acute stage were so variable that decisive changes in the cytological picture could not be recognized. Pennypacker (1954) has likewise found the study of nasal smears unrewarding in the same connexion.

Factors Influencing the Clinical Response

We have examined the data in some detail in relation to factors which may have a bearing on the clinical response. We have taken the 13 patients who responded to one or other dosage level as "responders" and regarded the others as "non-responders." We appreciate that this division is somewhat false, because not all patients who failed to respond to the first dosage level were put on to higher dosage. For this reason, as well as the small numbers involved, our inferences should not be regarded as conclusions, but only as clues worth pursuing in more formal later studies.

The age of the patient has little influence on the chance of responding to treatment, although the younger patients did slightly better than the older. The length of the history is possibly of greater importance, because five of the six patients with histories of less than seven years responded well.

The relationship of prophylactic pollen injections to the response to hemisuccinate nose-drops is not straightforward. Those patients who had experienced good results in previous seasons from pollen injections did well with the drops, six out of seven responding, compared with four out of eight among those who had received injections but without benefit, and three out of seven among those never treated by injections (Table I).

TABLE I.—*Relation Between Prophylactic Pollen Injections in Previous Seasons and Clinical Response to Local Hydrocortisone*

Pollen Injections in Previous Seasons	No. of Patients	No. Responding
Given with good response ..	7	6
.. .. poor	8	4
Never given	7	3

So far as pollen injections before the present season are concerned, patients who had had them did well with the nose-drops, five out of six responding, although, of course, the pollen injections had failed to prevent the occurrence of overt hay-fever. An interesting facet is that, whereas out of eight "responders" who had not received pollen injections in 1957 there were five who had chest symptoms during treatment, no chest symptoms complicated treatment in the five "responders" who had received such injections (Table II).

TABLE II.—*Liability to Chest Symptoms in the 13 Patients Responding Well to Local Hydrocortisone in Relation to Pollen Injections Before Current Season*

Pollen Injection Before Current Season	No. of Patients	Chest Symptoms
Given	5	0
Not given	8	5

The three factors which we tentatively suggest may increase the likelihood of a good response to hydrocortisone nose-drops—namely, a short history, previous good response to pollen injections, and pollen injections given before the current season—appear to be independent of one another.

Case 1

A male civil servant aged 32 had had severe hay-fever since 1950. In 1951 he had continuous nasal symptoms, worst in mid-afternoon and again during the night, from mid-May to end of July; "pollaccine" injections were ineffective. In 1953 skin tests were positive to grass and plantain. Mixed pollen injections gave an excellent result; these were repeated in 1954–6 with steadily diminishing effectiveness, but nocturnal symptoms never recurred. The season ran to the end of July in 1955 and 1956. He suffered badly from the side-effects of antihistamines.

Symptoms in 1957 Before Starting Treatment.—Mixed pollen injections were given, as previously, before the season. On June 10 he had an abrupt onset of continuous daytime running of eyes and nose, with nasal obstruction and heaviness, which persisted steadily. On June 19 the nasal mucosa was pale pink, lumpy, sticky, and crusted.

Treatment was begun on June 19 at a concentration of 1 mg./ml. After the first few hours he was symptom-free except for nasal irritability—that is, liability to sneeze once or twice on the slightest stimulus. He was fully normal on June 21. On reducing the dose on June 22 there was increasing coryza. On returning to the full dose on June 23 he became symptom-free. Treatment was continued until June 28, when the nasal mucosa was normal. Treatment was stopped.

A mild relapse began several days after June 28. After one day's further treatment he was again symptom-free for some days. A further one-day course was taken similarly in mid-July, with no further relapse.

Case 2

A golf professional aged 47 first had hay-fever in adolescence, following the subsidence of an asthmatic tendency as a child. He had severe and protracted coryzal attacks, building up rapidly on outdoor exposure from late May to end of June. Morning cough and sputum, with slight chest tightness, occurred when hay-fever was bad, usually in the later part of the season. In 1953–5 grass-pollen injections were given with good results. Major symptoms did not occur in 1956.

Symptoms in 1957 Before Starting Treatment.—He had mild symptoms from the end of May, and severe attacks began in the second week of June. Slight morning cough occurred after particularly bad days. On June 17 the nasal mucosa was sticky and unevenly oedematous, patchily pink, and red in colour.

From June 17 to 23 a concentration of 1 mg./ml. was given and he was free of nasal symptoms from the first day, except for bouts of "half a dozen sneezes" on some occasions on arriving at his place of work (as a golf professional). Morning cough became rather worse in the later part of the week and mild asthma occurred on the evening of June 23. The nasal mucosa was normal on June 24.

He had no further trouble, except for some mild nasal symptoms on June 26.

Discussion

The present study was intended to be a pilot one in order to form some preliminary judgments on the value of nose-drops containing a soluble compound of hydrocortisone in amounts unlikely to have any systemic action. It was hoped also to get some guidance on the best concentration to use if the treatment proved beneficial. The intention was to make use of such information in the design of more formal trials next season if the results looked encouraging.

In the event, hydrocortisone hemisuccinate sodium has proved to be a valuable treatment for about two-thirds of the patients treated, and we think it likely that better results will be obtained when it is possible to use higher concentrations than in the present study, in which their use was precluded only by technical reasons which will be avoidable in future.

The clinical response to this treatment has a distinctive quality. Improvement first reveals itself by the relief of those symptoms, such as nasal obstruction, which usually persist between the episodic coryzal attacks brought on by specific exposure or other irritation. Following this change, the episodic attacks become milder and shorter until they cease. The threshold of irritability of the nasal mucosa is the last feature to return to normal. This is the opposite of what happens with antihistamines, which diminish or suppress the coryzal attacks but often leave the patient with constant nasal discomfort, and, in some cases, with increased nasal obstruction. This difference in response suggests that

antihistamines quickly suppress certain components of the mucosal reaction but leave other components unchanged, whereas hydrocortisone produces a gradual change of the mucosa towards completely normal behaviour.

One feature of the results has both practical and theoretical implications. This is the finding that when the nose responds well to the nose-drops the concomitant eye irritation and chest symptoms commonly subside. This parallel change taking place in nose, eyes, and chest has been observed by other workers using hydrocortisone or prednisolone snuff in the treatment of hay-fever (Herxheimer and McAllen, 1956; Godfrey *et al.*, 1957). However, these workers were using enough of the corticoids to raise the possibility that the suppression of manifestations remote from the nose was due to a systemic action. In the present study a similar response was obtained with a daily dose of hydrocortisone which did not exceed 2 mg. in any of the patients concerned. Consequently, the possibility that these secondary manifestations of hay-fever were controlled by a systemic action of the hydrocortisone is remote. In other words, the improvement in the nasal mucosa was itself responsible in some way for the relief of eye and chest symptoms. This implies that these symptoms arose as a secondary consequence of the abnormal state of the nasal mucosa and were not due to the direct action of pollen on the organs concerned.

However, the issue is not clear-cut, because some of the patients who initially lost their chest symptoms developed them again later while on treatment, although the nose was normal. The secondary manifestations of hay-fever may therefore be of multiple pathogenesis. An important practical possibility is that a course of pollen injections before the current season, even when it has not prevented the onset of hay-fever, will protect the patient against a return of chest symptoms after his nose has responded to local hydrocortisone. These two methods of treatment may therefore prove to be complementary.

Leaving aside the question of giving pollen injections before the season, which requires further study, we are able to formulate a provisional plan for the use of local hydrocortisone hemisuccinate sodium in the treatment of hay-fever. This is possible because of two circumstances in the present study which largely compensate for its being uncontrolled. First, when local hydrocortisone is effective a definite improvement occurs within 24 hours, so that little time is lost if it turns out to be ineffective in a particular patient, even allowing for trying more than one concentration. Secondly, the decisive quality of the favourable responses left no doubt that the treatment was indeed efficacious, a conclusion arrived at the more readily because the hay-fever season coincided with a long spell of settled weather, so that external conditions altered little. We propose:

1. A solution containing hydrocortisone hemisuccinate sodium in a concentration equivalent to 2 mg. of free hydrocortisone per ml. should be used, two or three drops being applied to each nostril four times a day (the patient should be told how to use nose-drops efficiently).

2. If a good response is obtained treatment should be maintained for a few days after the nose has become symptomatically normal. The treatment can then be tailed off over a few days. (The only contraindication to maintaining treatment beyond the nasal response should be the development or recurrence of chest symptoms.)

3. After treatment has been stopped further recurrence of nasal symptoms will usually be aborted by one day's treatment.

Summary

Hay-fever subjects in a stage of symptoms have been treated with nose-drops containing hydrocortisone hemisuccinate sodium, a compound which is freely soluble in water.

Among 22 patients treated were 13 who showed a decisively favourable response, with the nose becoming normal in one to four days.

Eleven of these 13 patients responded to a concentration of 1 mg. per ml., with a maximum daily dose of 2 mg. of hydrocortisone. Five patients not responding to this concentration were treated with double this strength, and two responded. Thereafter, any recurrence of nasal symptoms responded to one day's treatment.

The nasal mucosa became macroscopically normal in those patients who responded well to treatment. Nasal smears did not yield helpful information.

Secondary manifestations of hay-fever, such as eye irritation and chest symptoms, usually subsided together with the nasal symptoms. However, chest symptoms sometimes recurred while the patient was under treatment with a normal nose, although they passed off again on stopping treatment, without immediate recurrence of nasal symptoms.

Factors tentatively suggested as improving the chance of a successful response to local hydrocortisone treatment were a short history of hay-fever (less than seven years); pollen injections in past years with good results; and pollen injections before the current season even though, as must be obvious, they had failed to prevent the occurrence of hay-fever.

Some practical and theoretical implications of the results are discussed and a provisional plan for the use of this form of treatment is formulated.

We are indebted to Glaxo Laboratories for making a gift of the nasal tablets.

ADDENDUM.—Since this article was written the provision of a tablet of hydrocortisone hemisuccinate sodium which is rapidly soluble, non-irritant, and non-deliquescent has proved to be technically difficult. The manufacturers have supplied us with slowly dissolving tablets which have proved satisfactory in non-seasonal allergic rhinitis. However, the answer to the problem may be the use of prednisolone phosphate, which is stable in aqueous solution as well as being highly soluble. In non-seasonal allergic rhinitis this compound seems to be roughly three times as active, weight for weight, as hydrocortisone hemisuccinate sodium.

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Worldfriends is a voluntary, non-political, and non-profit-making organization whose aim is to promote international friendship by group home-to-home exchanges. It is the British member of the World Friendship Federation, which has its headquarters in Copenhagen, and, through the parent body, has full consultative status with Unesco and Unicef. There are local branches of Worldfriends throughout Britain, and members entertain foreign visitors and in turn are entertained abroad. During the last 10 years over 26,000 young people from Britain and Western Europe have joined in Worldfriends holidays, enjoying free hospitality in each other's houses, and since 1953 an International Youth Fortnight has been held annually in London. This year 1,000 young visitors, aged between 14 and 20, from 16 different countries are expected in London from July 11 to 25. Anyone in the London area wishing to offer them accommodation, on a reciprocal basis, should write to the secretary, Worldfriends, 308, Earls Court Road, London, S.W.5.

HYPOGAMMAGLOBULINAEMIA AND TUBERCULOSIS

IMPLICATIONS OF THEIR ASSOCIATION, AND OTHER OBSERVATIONS

BY

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Hypogammaglobulinaemia, as an isolated serum-protein deficiency, is of current interest to clinician and immunologist alike. Present-day antimicrobial therapy prevents most patients with this defect from dying of the infections to which they are prone, and so there exists a " provocative experiment of nature "—as Good (1954) has called it—by which problems of immunity and hypersensitivity in man may be uniquely investigated. This is so because γ-globulin carries the majority of conventional serum antibodies measurable by currently available techniques, in addition to isohaemagglutinins.

Deficiency may be classified in this way : (1) Transient or physiological : found in infants aged 4 to 12 months and sometimes not rising to normal levels for 18 months (Gitlin and Janeway, 1956). (2) Congenital : a sex-linked, recessive, genetic inheritance of inadequate production of the protein fraction, affecting only males in the patients so far described, though inheritance allows its rare occurrence in females (Gitlin and Janeway, 1956). (3) Acquired : arising in older children and adults of either sex not previously afflicted by morbid frequency of infection, and, though it *appears* not to be inherited, an inherited defect may be manifesting itself in later life (Gitlin and Janeway, 1956). As γ-globulin (normal value, 600 to 1,200 mg./100 ml.) is not completely absent from the serum, being up to 25 mg./100 ml. in the congenital form and up to 100 mg./100 ml. in the acquired (Gitlin and Janeway, 1956), the term " hypogammaglobulinaemia " is used here rather than " agammaglobulinaemia." Both congenital and acquired forms appear to be permanent, and sometimes other protein fractions may also be deficient (Gitlin *et al.*, 1956).

By the middle of 1957 more than 100 cases of hypogammaglobulinaemia (congenital and acquired almost equally distributed) had been reported in the world medical literature, and among these were three patients with associated tuberculosis. The implications of this association and other incidental features are the subject of this paper, which includes a report of a patient with pulmonary tuberculosis.

Case Report

The patient, an unmarried woman aged 22, was the only child in an average working-class home. There was nothing significant in the family history.

Clinical History.—A forceps delivery, she was healthy until about 4 years of age, when recurrent " colds "—usually with cough—started, obviously being more frequent than in other children. Minor convulsions were also observed, and a year later typical grand-mal epilepsy, with approximately one seizure daily, had developed. From then on she was never free from colds ; yellow nasal discharge and cough with yellow sputum (sometimes subject to acute increase with fever) were almost always present, and sties abnormally common. From the age of 10 grand-mal seizures increased in frequency and severity.

Between 1949 and 1955 she had (apart from almost continuous symptoms of chronic bronchitis) severe streptococcal sore throat, repeated indolent furunculosis, six episodes of lobar or segmental pneumonia associated with undue prostration which resolved with antimicrobial therapy, empyema of the maxillary antra, a heavy infection of mouth and pharynx with *Candida albicans*, appendicectomy for an acutely inflamed appendix (not examined histologically), and a large abscess in the buttock. Most bacterial infections were accompanied by moderate leucocytosis. In 1952, when 17, she was ill with aplastic anaemia (probably due to the anticonvulsant drug troxidone, which was withdrawn) and was treated with multiple blood transfusions and antibiotics for about three months.

In 1954, after haemoptysis, she was found to have pulmonary tuberculosis, with positive sputum, and treatment with streptomycin and isoniazid was instituted. In 1955 she entered Harefield Hospital, when she was febrile and exceptionally lethargic, and antituberculous treatment was continued. Over the next twelve months she had three lower segmental non-tuberculous pneumonias, recurrent indolent furunculosis, non-tuberculous cystitis, offensive vaginal discharge, present for many months, and bilateral middle-ear deafness without evidence of labyrinthine damage. Petit mal occurred frequently daily, though grand-mal seizures showed little change.

Hypogammaglobulinaemia was diagnosed in May, 1956, and in August therapeutic replacement of γ-globulin was begun.

Clinical Examination (in Harefield Hospital).—The tuberculous upper-lobe consolidation in the right lung which was present on admission resolved over a period of six months. At no time were lymph nodes, liver, or spleen enlarged.

Investigations.—(1) *Plasma Proteins :*—April, 1956 : γ-globulins absent on paper electrophoresis and Kunkel's zinc sulphate turbidity test ; fractional precipitation values between 60 and 120 mg./100 ml. December : 320–340 mg./100 ml. February, 1957 : 320 mg./100 ml. by precipitin diffusion method. Albumin, α_1,α_2, and β globulins, normal values. Fibrinogen, 0.18 g./100 ml. (normal, 0.2 to 0.4 g./100 ml.). (2) *Haematology :*—Morphology and numerical values of peripheral blood cells always normal, except for moderate neutrophil leucocytosis during bacterial infections. Group A1, Rh positive, R1 R1 (CDe/CDe). Isohaemagglutinins absent. A and H secretor substances in saliva. (3) *Vaginal discharge* revealed occasional *Staph. aureus* but no monilia or *Trichomonas vaginalis*. No plasma cells. (4) *Sputum* was usually purulent, and contained many neutrophil leucocytes but no plasma cells. *H. influenzae* grown on a few occasions. In December, 1955, and March, 1956, two cultures were tubercle-positive ; 28 cultures negative thereafter. (5) *Tuberculin Tests :*—April, 1956, K.O.T. 1 : 1,000 positive (induration, 2 cm. ; erythema, 3.5 cm.). September, K.O.T. 1 : 100 positive (induration, 1.5 cm. ; oedema, 3 cm. ; erythema, 6 cm.). (6) *Schick and Dick Tests* were negative on two separate testings (the patient was never immunized against diphtheria). (7) *Electroencephalograms :*—August, 1956, pronounced epileptic pattern with generalized high-voltage discharges.

Chest *x*-ray films in 1949 to 1956 showed various transient middle and lower lobar consolidations. Right upper lobe tuberculous consolidation and collapse (1954) cleared slowly, though without proper re-expansion. No hilar node enlargement ever seen. Bronchograms in December, 1956, showed moderately severe " saccular " bronchiectasis of anterior and apical segments of the right upper lobe. *Otherwise the bronchial tree appeared entirely normal.*

Treatment.—Streptomycin, 1 g. daily, with isoniazid, 300 mg., for 14 months, and various other antimicrobial agents for non-tuberculous infections were often required for periods of many weeks. Intramuscular administration of γ-globulin was started in August, 1956 (almost two years after tuberculosis was diagnosed), the dosage schedule (according to a Medical Research Council therapeutic trial in which this patient was included) being 0.5 g./kg. body weight in one week as a loading dose ; followed by 0.025 g./kg./week for four months ; and from December, 1956, 0.5 g./kg./

week for another four-months period. It was convenient to spread injections over five days in the week. Methoin and phenobarbitone were given in small daily doses as anticonvulsants.

Diagnostic Criteria and Treatment

Acquired hypogammaglobulinaemia was diagnosed on the grounds of the history (continued bacterial infection probably starting when the patient was about 5, and nine episodes of bacterial pneumonia in six years), γ-globulin deficiency on paper electrophoresis, zinc sulphate turbidity tests, and fractional precipitation; and the absence of isohaemagglutinins. The criteria for active pulmonary tuberculosis, which developed some years after the estimated onset of hypogammaglobulinaemia, were development under observation, haemoptysis, two sputum cultures positive for tubercle bacilli, and normal resolution with anti-tuberculous drug therapy.

Treatment of patients with hypogammaglobulinaemia involves antimicrobial agents and the permanent replacement of γ-globulin, the usual dose being 0.1 g./kg./month. Prolonged antibiotic prophylaxis (for example, with tetracycline) has been recommended (Mazzitello and Good, 1956). The antimicrobial agents given for non-tuberculous infections in this patient invariably succeeded, but, before γ-globulin therapy, more slowly than in normal individuals. After six months' replacement of γ-globulin its serum level had increased more than threefold; though little change was observed on paper electrophoresis.

After three months' γ-globulin therapy the patient was animated and cheerful, when previously she had been dull and lethargic; and both she and her parents said she had never been so well. Respiratory infections and frequent inexplicable low-grade fevers no longer occurred. Nasal discharge and purulent sputum practically ceased, but indolent skin infections still gave trouble despite antibiotics.

Hypogammaglobulinaemia and Epilepsy

After some months of γ-globulin therapy fewer grand-mal seizures occurred and petit-mal episodes were rarely observed; electroencephalograms were impressively better, though no change in anticonvulsant drugs had been made for more than 18 months. In spite of this striking improvement there is no apparent connexion in this patient between hypogammaglobulinaemia and epilepsy.

Reticulo-endothelial System and Hypogammaglobulinaemia

Plasma cells are the chief source of γ-globulin and bacterial antibodies (Craig *et al.*, 1954; Coons *et al.*, 1955; Good and Varco, 1955), though the role of lymphocytes has not been fully clarified (Sundberg, 1955). In congenital and acquired hypogammaglobulinaemia plasma cells are absent or extremely sparse in pus, lymph nodes, and bone marrow, and were not found in inflammatory products of this patient. In addition, abnormal enlargement of lymph nodes, liver, and spleen, separately or together, have been reported in some cases of the acquired deficiency only (Rohn *et al.*, 1955; Good and Mazzitello, 1956; Citron, 1957); and, occasionally, a thymoma has been discovered (Good and Varco, 1955; Martin *et al.*, 1956; MacLean *et al.*, 1956; Ramos, 1956), removal of which did not alter the serum γ-globulin level in one patient (MacLean *et al.*, 1956). Such abnormalities were not present in my patient, but they have been found associated with granuloma or tumour involvement of the reticulo-endothelial system in some patients—sarcoidosis (Zinneman *et al.*, 1954), malignant lymphoma (Arends *et al.*, 1954), chronic lymphatic leukaemia (Prasad and Koza, 1954; Jim and Reinhard, 1956), as well as generalized amyloidosis (Gras *et al.*, 1954)—and it may well be that such involvement directly impairs plasma-cell function and therefore antibody formation. It is probable that acquired hypogammaglobulinaemia is more commonly due to immaturity of plasma cells, as instanced by Citron (1957), and this may be genetically determined.

The immediate question is: Can tuberculosis cause hypogammaglobulinaemia by widespread involvement of the reticulo-endothelial system? At present no evidence supports this, and the frequency of tuberculosis in hypogammaglobulinaemic patients has, to date, been similar to that in the general population. The association of the two conditions is probably coincidental. My patient's history suggested the presence of hypogammaglobulinaemia some years (five at least) before pulmonary tuberculosis developed.

Neutropenia or lymphopenia, which may reflect reticulo-endothelial dysfunction, is found in some patients (Good and Varco, 1955), but was not found in mine. Perhaps such findings are sometimes due to heavy infection depressing blood-cell formation.

Bacterial Infections other than Tuberculosis

Hypogammaglobulinaemia is apt to reduce bacterial immune response, and abnormally frequent, and often severe, infections at any site with both Gram-positive and negative organisms occur (Mazzitello and Good, 1956). Pneumonia, bronchiectasis (a common finding), and infection of the gastro-intestinal tract simulating ulcerative colitis or steatorrhoea are found more often in the acquired form (Gitlin and Janeway, 1956), but this patient had no bronchographic evidence of bronchiectasis other than in the right upper lobe, which was not unexpected after its long-standing collapse. It may be that acquired hypogammaglobulinaemia will be found in a few bronchitic patients, and this is even more likely in young patients with bronchiectasis. Steatorrhoea was not observed in my patient, and although it has been described with acquired hypogammaglobulinaemia (Sanford *et al.*, 1954; Rohn *et al.*, 1955; Rosecan *et al.*, 1955; Zinneman and Hall, 1956; Cooke *et al.*, 1957), it is more likely that bacterial infection of the bowel, rather than an intrinsic anomaly of fat absorption, explains the symptoms.

Otitis media, common in these patients but unrecognized in the present one, appeared to have caused her bilateral middle-ear deafness.

Fungus and Virus Infections

Hypogammaglobulinaemia does not seem to cause undue susceptibility to fungus infection, but administration of certain antibiotics may lead, as in normal individuals, to development of monilial infection (Mathias and Rees, 1956); and this is the most likely explanation of the *Candida albicans* infection of mouth and pharynx in this patient. There is, however, some evidence that γ-globulin deficiency (either transient or congenital) may be aetiologically related to *Pneumocystis carinii* pneumonia in early childhood (Hutchison, 1955; Bird and Thomson, 1957), and further study of this will be of interest.

Virus infections are no more frequent in hypogammaglobulinaemic patients than in normal individuals, and they follow an expected course. Virus antibodies are not found in these patients' serum, nor is it possible to produce them with virus antigens (Good and Varco, 1955). Immune response to virus infection, therefore, unlike that to bacterial infections, may be either wholly or partly independent of γ-globulin, or may be mediated through minute quantities of it, through the α-globulin fraction of plasma proteins, or through some purely cellular mechanism (Raffel, 1956).

Tuberculosis

The reported cases of tuberculosis associated with hypogammaglobulinaemia are one of tuberculous lymphadenitis (Veterans Administration, 1955); one of inactive pulmonary tuberculosis with acute tuberculous lymphadenitis and apparent steatorrhoea (Zinneman and Hall, 1956); one of primary pulmonary tuberculosis with tubercle bacilli in gastric washings (Elphinstone *et al.*, 1956); and one of primary tuberculosis in a child (cited by Zinneman and Hall, 1956), which has not been authenticated (Zinneman,

personal communication, 1957). The first two had the acquired deficiency, the second two the congenital. My patient appears to be the second recorded with active pulmonary tuberculosis.

As almost all the earlier described cases of hypogammaglobulinaemia were tuberculin-negative, it was originally thought that all such patients would *not* possess delayed tuberculin hypersensitivity as shown by positive skin tests with old tuberculin or P.P.D. (Young *et al.*, 1955), though not all those reported have been tested. Nevertheless, a skin test has been found to be *positive* in at least three patients (Lang *et al.*, 1954; Elphinstone *et al.*, 1956; Zinneman and Hall, 1956), and is clearly demonstrated in my patient. Furthermore, B.C.G. can induce delayed tuberculin sensitivity in patients with hypogammaglobulinaemia (Kulneff *et al.*, 1955; Porter, 1955).

Since Chase (1945, 1946) demonstrated that the delayed type of specific cutaneous sensitivity to tuberculin can be transferred to *insensitive* guinea-pig recipients by injections of leucocytes drawn from *sensitive* donor guinea-pigs, others —notably Lawrence (1949, 1955), Urbach *et al.* (1952), Good and Varco (1955), and Porter (1955)—have transferred delayed tuberculin sensitivity from sensitive human donors by intradermal injections of their *washed* leucocytes into insensitive human recipients. And Good *et al.* (1957) have, by the same method, conveyed such sensitivity (which has persisted so far for two years) from sensitive donors to insensitive recipients; while, even more strikingly, Porter (1955) has transmitted tuberculin sensitivity from a child with congenital hypogammaglobulinaemia, in whom it was produced by B.C.G., to a normal insensitive subject. Although leucocytes employed in these transfer techniques are injected intradermally, Schlange (1954) has claimed that delayed tuberculin sensitivity was induced in a tuberculin-negative (insensitive) infant (with erythroblastosis foetalis) by whole blood transfusion.

It is not known how an injection of a few sensitized donor leucocytes causes human recipients to respond to specific test substances in the same manner as did the donor following natural infection (Lawrence, 1956); and the chemical nature of the "transfer factor" is unknown (Lawrence, 1956), though it can survive certain enzyme action (Lawrence, 1955) and be set free from sensitized leucocytes by interaction with specific antigen (Lawrence and Pappenheimer, 1956, 1957). It should be added that production of delayed hypersensitivity to tuberculin and other bacterial antigens in a previously insensitive hypogammaglobulinaemic patient has been achieved by subcutaneous homograft of lymph nodes from a sensitized human donor (Martin *et al.*, 1957).

Just as tuberculin sensitivity apparently behaves normally in patients with hypogammaglobulinaemia, so the acquired immune response to tuberculous infection (judged by the clinical course) appears no different in these patients from that in normal individuals: at least, in my patient (in whom tuberculosis was known to have existed for two years before γ-globulin therapy began) and those reported to date. Indeed, such infection has followed a normal pattern of behaviour without tendency to fulminate or spread; and, so far, B.C.G. injections have caused no evidence of tuberculous disease (Kulneff *et al.*, 1955; Porter, 1955; Elphinstone *et al.*, 1956), and are possibly without danger.

Baldwin and Iland (1953) demonstrated an increase in serum γ-globulin in normal subjects with active tuberculosis, and, although it contained complement-fixing antibodies in advanced disease, they could find no antibody to the tubercle bacillus in the increased fraction; but Pescetti and Orlandi (1956), using a modified technique, produced contrary evidence indicating that γ-globulin may carry tuberculous antibodies. This discrepancy may be due to experimental method. But the fact remains that *clinically* the immune response to tuberculosis can function normally in the presence of isolated γ-globulin deficiency; and Raffel (1955) states that, experimentally, a cellular mechanism may be responsible for acquired immunity rather than the acquisition of antibodies, as measured by present techniques. It is not known what place natural non-antibody protective substances found in the serum, such as properdin (Pillemer *et al.*, 1954), may have; but in one patient with tuberculosis and hypogammaglobulinaemia (Veterans Administration, 1955) this substance was absent: it is uncertain whether it is linked to γ-globulin.

Sensitivity to Diphtheria and Streptococcal Antigens

Schick and Dick tests have invariably been found positive in patients with hypogammaglobulinaemia, and attempts to produce antibodies to diphtheria and streptococcal toxins in such patients have failed (Good and Varco, 1955). There is abnormal susceptibility to infection with these organisms. Using the leucocyte transfer technique, Lawrence (1952, 1955) and Lawrence and Pappenheimer (1956) have transferred delayed skin sensitivity to diphtheria toxin and streptococcal antigens from sensitized normal human donors to unsensitized normal human recipients. But they were unable to detect any serum antibody of conventional type to diphtheria toxin (Lawrence and Pappenheimer, 1956). It seems likely that, although leucocytes may normally play some part in the development of delayed hypersensitivity, the serum antibody response to these two infections is mediated chiefly by γ-globulins, as it may be to all bacterial infections other than tuberculosis.

Atypically, in this patient both Schick and Dick tests were *negative* (although she had never had diphtheria immunization) and indicated the presence of delayed sensitivity to the appropriate antigens. A possible explanation is that this was induced by cell transfer in the blood transfusions she received four years previously—a process that might be predicted from the observations already quoted, but is not proved.

Conclusions

Hypogammaglobulinaemia in man offers a remarkable natural experiment for the study of delayed hypersensitivity and serum antibody response to tuberculosis. Both appear to function normally in patients suffering this deficiency, so that in normal individuals the two phenomena may be independent of γ-globulin and may be to a large extent related to cellular mechanisms. This theory is reinforced, in the case of hypersensitivity, by leucocyte transfer experiments, and Pappenheimer (1955) has made the interesting suggestion that sensitized leucocytes may, in the presence of antigen, liberate "transfer factor," which is then ingested by non-sensitized leucocytes, and so set up a "biological chain reaction" maintaining hypersensitivity.

An α-globulin fraction analogous to that discovered in guinea-pigs by Cole and Favour (1955), and shown to transfer delayed tuberculin sensitivity in these animals, may exist in man, but has not yet been demonstrated. Hence, this fraction or one or more of the other fractions may yet be shown to possess antibody activity to antigens of the tubercle bacillus in man.

On the other hand, in individuals with hypogammaglobulinaemia, delayed hypersensitivity to diphtheria and streptococcal antigens does not develop naturally, though it can be evoked by leucocyte transfer; and immune response is absent, or very feeble, and cannot be induced experimentally. From the clinical and immunological evidence provided by hypogammaglobulinaemic patients, all bacterial infections (other than tuberculosis) appear to behave similarly.

Immunologically tuberculosis appears to stand alone among bacterial infections, though leprosy may show similar behaviour; for, from preliminary observations, there seems to be no correlation between serum γ-globulin levels (electrophoretically determined) and activity of conventional serum antibody in patients with lepromatous disease (Mayama, 1954).

The foregoing is likely to be oversimplified, for improved analysis may reveal new protein fractions and functions. Hypersensitivity and immune response to tuberculosis may then be found to be shared by leucocytes (and other body cells) and some serum protein fraction other than γ-globulin. In short, there may be some combined function of leucocytes and serum proteins.

The door is open to a more comprehensive conception of the immunology of tuberculosis.

Summary

A case of acquired hypogammaglobulinaemia, active pulmonary tuberculosis, and epilepsy is reported, and reference is made to the other recorded cases of hypogammaglobulinaemia associated with tuberculosis.

It is submitted that the association of hypogammaglobulinaemia and tuberculosis is coincidental, and that they bear no aetiological relationship one to the other.

The natural course of tuberculous disease appears to be unaffected by hypogammaglobulinaemia, and delayed hypersensitivity and immune response are normal in patients observed to date.

It is suggested that delayed hypersensitivity and serum antibody response to tuberculosis function independently of γ-globulin, and may rely on a cellular mechanism (leucocytes and other body cells), though the possibility of an unidentified serum protein fraction sharing such immunological powers is not excluded.

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ADDENDUM.—Since this paper was completed I have encountered another patient, similar to mine, at Bellevue Hospital, New York City. A man of 28, with a history of recurrent pneumonia and other infections since the age of 6 months, had bronchiectasis and recently developing pulmonary tuberculosis. Sputum grew tubercle bacilli on four different occasions, and P.P.D. skin tests (second strength) were positive (with induration) on three occasions. No enlargement of lymph nodes, liver, or spleen was ever apparent. Chest *x*-ray films showed bilateral but not extensive upper-lobe disease. Hypogammaglobulinaemia was revealed by serum electrophoresis and fractional precipitation. Tuberculosis followed the expected satisfactory course on antituberculous drugs. He did not receive γ-globulin replacement therapy.

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CLINICAL STUDIES ON THE ACTION OF BEMEGRIDE IN BARBITURATE OVERDOSAGE*

BY

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Since bemegride (ββ-methylethylglutarimide) was introduced by Shaw *et al.* in 1954, there has been much discussion on whether this drug is a specific antagonist to the barbiturates or a non-specific central analeptic. Many papers have described the stimulating effect of bemegride in barbiturate coma (Shulman *et al.*, 1955; Clemmesen, 1956), but more recent reports have suggested that it appears to have a restorative action in coma due to non-barbiturate sedatives, such as primidone (Dotevall and Herner, 1957) and glutethimide (Rowell, 1957). The factors which influence the outcome in patients suffering from sedative poisoning are so varied that it is impossible to assess the specificity of action of bemegride in such circumstances.

The use of thiopentone in general anaesthesia, however, might appear to provide a suitable background for the study of the action of bemegride in man. Harris (1955), Canbäck *et al.* (1955), and Bentel *et al.* (1956) have reported that 50–100 mg. of bemegride injected intravenously could rapidly terminate anaesthesia induced by 0.5 g. of thiopentone. In these studies the premedication drugs varied, as did the duration of administration of the anaesthetic; no control observations were made.

The pilot study reported here reveals some of the difficulties in demonstrating the antibarbiturate activity

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of bemegride in man. The technique is a modification of that described by Harris (1955).

Method of Pilot Study

Observations were made on 20 women undergoing minor gynaecological operations. Each received 1/100 gr. (0.6 mg.) of atropine sulphate 45–60 minutes before induction of anaesthesia with 0.5 g. of thiopentone, the anaesthesia being maintained with nitrous oxide and oxygen. At the end of the operation 10 ml. of unlabelled solution (either normal saline or 50 mg. of bemegride) was injected intravenously. The nature of the injection given to any one patient was not known to the observer. In an attempt to assess the level of consciousness, repeated examinations of the palpebral and tendon reflexes were made and the response to painful stimuli was noted. It was found that such methods of grading levels of consciousness were unreliable, as positive results were not obtained in a definite sequence and the responses were liable to observer error. The patient's ability to respond to questioning was therefore accepted as the criterion of being awake. The interval between the injection and awakening was recorded for each patient and named the "wakening time."

Results of Pilot Study

These results are summarized in the Table. Of the 20 patients, 11 received bemegride and 9 saline. Seven who received bemegride responded to questioning in 1.5 to 5

Wakening Times in 20 Patients After Injection of 50 mg. of Bemegride or Normal Saline

Case No.	Weight		Duration of Operation (Minutes)	Nature of Injection	Wakening Time (Minutes)
	lb.	kg.			
1	135	61·2	11	Bemegride	1·5
2	106	48·1	5	,,	5
3	113	51·3	16	,,	5
4	105	47·6	7	,,	5
5	119	54·0	10	,,	1·5
6	146	66·2	8	,,	3
7	121	54·9	8	,,	4
8	135	61·2	9	,,	12+
9	117	53·1	6	,,	8+
10	119	54·0	4	,,	6+
11	142	64·4	18	,,	8+
12	111	50·3	10	Saline	1·5
13	168	76·2	11	,,	2·5
14	139	63·0	3	,,	4
15	104	47·2	7	,,	3
16	90	40·8	14	,,	3
17	119	54·0	9	,,	2
18	128	58·1	11	,,	1·5
19	117	53·1	8	,,	6+
20	113	51·3	17	,,	6+

minutes (mean, 3.6 minutes); of those who received saline, seven were awake in 1.5 to 4 minutes (mean, 2.5 minutes). There is no significant difference between the wakening times of the groups.

In this type of study the durations of administration of anaesthesia should be comparable in the two groups. In this instance they were similar, the mean durations in the bemegride and saline groups being 9.2 and 9.9 minutes respectively (see Table). There was no apparent relationship between the weight of the patient, the "wakening time," and the interval between the time of thiopentone administration and wakefulness (see Table).

This pilot study, employing the "double-blind" technique, does not substantiate the published claims based on similar trials (Harris, 1955; Canbäck *et al.*, 1955; Bentel *et al.*, 1956). It demonstrates that such an approach cannot provide objective evidence on whether or not bemegride is a specific barbiturate antagonist; the patient may already be in the phase of natural recovery before the drug under trial is given.

Clinical pharmacological studies of hypnotics and analeptics often lack precision because of the difficulty in knowing the exact moment when the subject becomes awake. There is a transitional phase between sleep and wakefulness. An objective method of recording this phase would be valuable. It was decided therefore to see if the electroencephalogram would provide more precise information on the "wakening time."

E.E.G. Experiment on Wakening Time

Continuous E.E.G. recordings were made on subjects asleep after sodium amylobarbitone, and the arousing effect of bemegride was observed. Eight men aged 22–55 years volunteered for the experiment. In the fasting state, each swallowed 9–15 gr. (0.6–1 g.) of sodium amylobarbitone over a period of one and a half hours. While drowsy, an intravenous drip infusion of physiological saline was started, and this was continued throughout the period of observation. Scalp electrodes from an eight-channel Ediswan electroencephalograph were placed in position and E.E.G. (bipolar) recordings taken at intervals during the experiment. The patient lay undisturbed on a couch until he was clinically "asleep" and the E.E.G. tracing showed a consistent deep sleep pattern. Then 50 mg. of bemegride in saline solution was injected rapidly into the rubber tubing of the infusion apparatus close to the needle. Both the patient and the continuous E.E.G. records were observed carefully. If there was no change in either within two minutes, a further 50 mg. of bemegride was injected.

A note was made on the E.E.G. tracing at the time of the first sign of arousal. Each patient was then examined with special reference to his mental alertness, memory for recent events, gait, and muscular co-ordination. The E.E.G. records were studied for evidence of deep sleep pattern and barbiturate activity; the first change in the pattern after the injection of bemegride was noted and its time relationship to the first clinical sign of arousal recorded.

Results of E.E.G. Experiment

Each subject wakened after the administration of bemegride. A brief description of one patient will illustrate the clinical state, which was similar in all. After opening his eyes and grimacing, he gazed drowsily at his surroundings and within a few seconds began to speak. Speech was slurred, and this dysarthria persisted sometimes for 10 hours. There was diplopia on viewing near objects for 10 minutes after wakening. His memory for events preceding the experiment was normal. His gait was ataxic. Objectively the clinical state closely resembled that of moderate alcoholic intoxication. If placed in favourable surroundings the patients relapsed into sleep within 30 minutes and did not waken spontaneously until up to 16 hours later.

The E.E.G. pattern in each subject was that of deep sleep; in addition, three showed barbiturate activity. When bemegride was given, the deep sleep rhythm on the E.E.G. continued unchanged until the moment when the patient moved and wakened. The rhythm immediately reverted to normal (see Fig. 1). The E.E.G. records gave no indication that wakening was about to occur. In the four patients who required a total of 100 mg. of bemegride to cause arousal there was no premonitory change in the E.E.G. tracings in spite of increasing body levels of bemegride. In none of those showing barbiturate activity was this dispelled by bemegride.

Fig. 2 shows the persistence of fast barbiturate waves after the patient (Case 7) awoke. The normal resting record for this patient is shown in Fig. 3.

Discussion

This technique clearly demonstrates that bemegride will waken subjects asleep after sodium amylobarbitone. On arousal, however, such patients do not have normal muscular co-ordination and their emotional state is labile. For his personal safety each patient in this study required close supervision for at least six hours after wakening or until he had relapsed into sleep. It is probable that the state of intoxication was due to sodium amylobarbitone; three further volunteers who did not sleep after ingesting 15 gr. (1 g.) of this drug and who were not given bemegride presented a very similar picture.

It had been hoped that the E.E.G. record would give objective evidence of the onset of the transitional phase between sleep and wakefulness; that the rhythm would revert to normal before the patient awoke. This did not occur. Clinical observation gave as early information as did the E.E.G.

Two patients admitted to hospital in barbiturate coma were given bemegride, and their course was followed by intermittent E.E.G. recordings. Each patient returned to consciousness while on treatment with bemegride, but the E.E.G. records gave no indication of the depth of coma, and indeed evidence of barbiturate activity on the E.E.G. persisted for many hours after the patient wakened. This confirms the findings of Peacock (1956).

The E.E.G. evidence might suggest that bemegride is not a specific barbiturate antagonist, but the site of action of sodium amylobarbitone may be principally in the hypothalamus, as may also be that of bemegride. The E.E.G. records only electrical potential changes in the cerebral cortex.

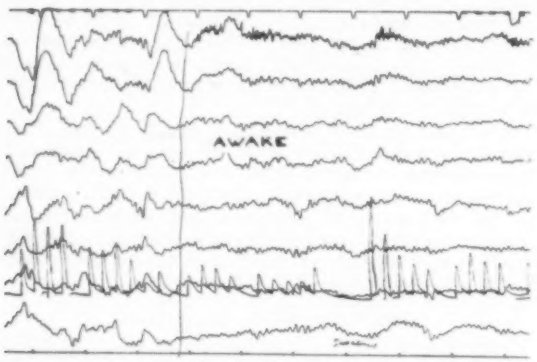

FIG. 1.—E.E.G. record showing change in pattern coinciding with clinical arousal.

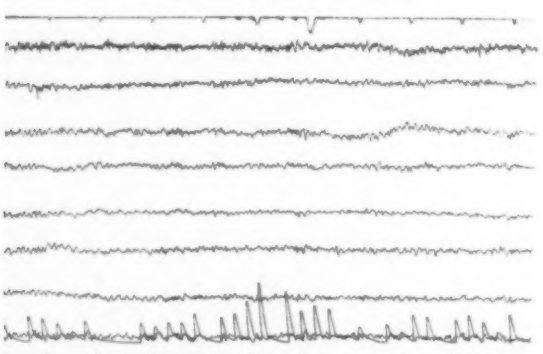

FIG. 2.—Persistence of barbiturate activity in Case 7 after wakening.

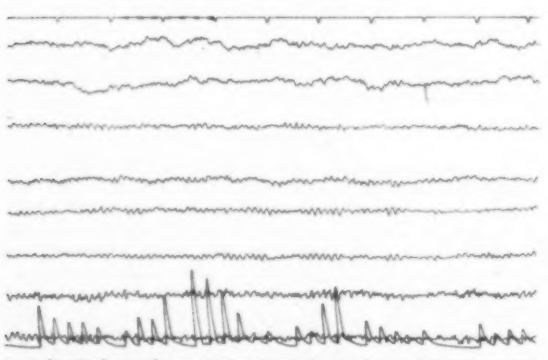

FIG. 3.—Normal resting E.E.G. record for Case 7.

Summary

The effects of bemegride and saline in terminating thiopentone anaesthesia in 20 women were compared, using the "double-blind" technique. There was no significant difference in the "wakening times" after either substance. The fallacies of using such a method to evaluate the action of bemegride are stressed.

Continuous E.E.G. records were taken in eight volunteers who were roused with bemegride from sleep induced by sodium amylobarbitone. The E.E.G. pattern of deep sleep did not alter until the subjects wakened. In three patients who showed barbiturate activity on the E.E.G. this was not dispelled by bemegride.

The significance of these findings is briefly discussed.

I thank Dr. D. McKay Hart for permission to study the gynaecological patients; Dr. O. Watt, who administered the anaesthetics; and Dr. S. Renfrew, Mrs. I. S. Haggar, and Miss M. Watson, of the E.E.G. department of the Glasgow Royal Infirmary, for their co-operation and guidance. My thanks are also due to the volunteers.

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A COMPARISON OF MATERNAL AND FOETAL FOLIC ACID AND VITAMIN B_{12} AT PARTURITION

BY

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In a previous study comparing folic acid (P.G.A.) and vitamin B_{12} during normal pregnancy (Baker *et al.*, 1957) it was reported that maternal vitamin B_{12} blood levels were low and P.G.A. levels high. Recent studies on the vitamin B_{12} serum levels in mothers and infants at delivery show that maternal levels decline through pregnancy and infant levels are approximately twice that of the mother (Okuda *et al.*, 1956; Boger *et al.*, 1957; Dumont, 1957). Since both P.G.A. and vitamin B_{12} play significant parts in pregnancy and foetal development (O'Dell *et al.*, 1951; Nelson *et al.*, 1956; Nelson and Evans, 1956), a comparison of vitamin B_{12} and P.G.A. serum levels in mothers and infants at parturition was carried out.

Methods.—Vitamin B_{12} assays on maternal and infant serum were carried out in parallel with ***Euglena gracilis*** and *Ochromonas malhamensis* by methods previously described (Hutner *et al.*, 1956; Baker *et al.*, 1956). The P.G.A. levels were assayed with a thermophilic bacillus (Baker *et al.*, 1955, 1957). Maternal blood was collected from an antecubital vein at the time of delivery. Infant blood was obtained from the cord. Samples were collected from 113 patients admitted to the obstetrical service of the Mount Sinai Hospital.

Results

The results are given in Table I. The median value of 190 μμg. of vitamin B_{12} per ml. in the maternal serum is lower than that of 390 μμg./ml. in infant serum. The same relationship is shown for P.G.A. levels; the median

TABLE I.—*Vitamin B_{12} and P.G.A. Content of Maternal and Infant Blood*

Quartile	Vitamin B_{12} (μμg./ml.)		P.G.A. (mμg./ml.)	
	Maternal	Infant	Maternal	Infant
1st	25–120	35–250	1–4	1–9
2nd	120–190	200–390	4–7·5	9–40
3rd	190–270	390–600	7·5–22·5	40–90
4th	>270	>600	>22·5	>90
Median	190	390	7·5	40
No. of patients ..	104	70	67	38

in maternal serum is 7.5 mμg./ml., and in infant serum 40 mμg./ml. A total of 104 specimens of maternal blood and 70 samples of cord blood were assayed for vitamin B_{12}; 67 maternal and 38 infant samples were assayed for P.G.A. Only 14% of the infant blood showed vitamin B_{12} values below the median of the mothers. Likewise, 26% of the infant blood fell into the P.G.A. 0–10 mμg./ml. range, which comprises 66% of the maternal samples.

In Table II a total of 22 paired mother and infant vitamin B_{12} and P.G.A. levels are listed. Except for two cases (Nos. 17 and 22) the vitamin B_{12} and P.G.A. levels in infant blood are higher than in the corresponding maternal serum.

TABLE II.—*Paired Mother and Infant P.G.A. and Vitamin B_{12} Serum Values**

Patient No.	Mother		Infant	
	Vitamin B_{12}	P.G.A.	Vitamin B_{12}	P.G.A.
1	53	3	115	4
2	80	2·5	310	3·5
3	90	1	330	3·5
4	100	5	270	11
5	121	5·5	225	51
6	125	2	325	5
7	128	7	246	41
8	135	5	250	50
9	165	2	650	5·5
10	170	2	1,150	5·5
11	180	5	300	100
12	200	2·5	334	12
13	200	100	450	120
14	200	100	770	250
15	217	5	437	41
16	233	8	265	9·5
17	250	50	150	200
18	250	33	250	100
19	250	100	600	150
20	300	3	390	100
21	350	27	700	60
22	550	11	120	3·5

* Vitamin B_{12} values given μμg. ml., P.G.A. in mμg./ml.

Discussion

Vitamin-B_{12} levels in the serum decrease throughout pregnancy (Boger *et al.*, 1956). The higher infant blood levels (Table I) suggest that during this state the foetus draws upon maternal vitamin-B_{12} stores, causing a temporary vitamin-B_{12} depletion in the mother. This is in agreement with reported results (Karlin and Dumont, 1955; Okuda *et al.*, 1956). Vitamin B_{12} is essential for proper metabolic functions in man and animals (Jukes and Williams, 1954); the part it plays in foetal growth and tissue nucleic acid synthesis is of primary significance. Animals deficient in vitamin B_{12} give birth to hydrocephalic young (O'Dell *et al.*, 1951) with a high incidence of skeletal abnormalities (Grainger *et al.*, 1954). The nucleic acid content of the tissues also becomes altered (Bruemmer *et al.*, 1955). The interrelationship between vitamin B_{12} and P.G.A. in nucleic acid synthesis (Mueller and Will, 1955) explains the foetal needs for these two vitamins. As in the case of vitamin B_{12}, the foetus draws P.G.A. from the maternal circulation, lowering the amount of circulating P.G.A. (Tables I and II).

Another role of P.G.A. lies in its effect on hormonal responses (Baker *et al.*, 1957). P.G.A. antagonists inhibit progesterone activity and cause foetal death. These actions are overcome by P.G.A. (Thiersch and Philips, 1950; King and Velardo, 1951). At parturition the elevated progesterone level noted during pregnancy falls (Pearlman, 1954); at this time the P.G.A. levels also fall (Baker *et al.*, 1957) (Table I). These observations suggest an interrelated action between progesterone and P.G.A. during pregnancy; at term this action ceases. The ability of P.G.A. to overcome the adverse effects of P.G.A. antimetabolites on progesterone activity, and its action in catalysis of varied essential synthetic processes, make P.G.A. important for normal pregnancy and foetal viability.

The paired samples of mother and infant serum (Table II) illustrate the differentials in vitamin B_{12} and P.G.A. at delivery. In some cases the infant vitamin-B_{12} and P.G.A. levels are over four times as high as those of the mother. The high infant P.G.A. and vitamin-B_{12} serum levels explain the stress imposed by pregnancy on maternal metabolism and indicate the avidity of rapidly growing foetal tissues for these vitamins.

Summary

A comparison of vitamin B_{12} and P.G.A. serum levels of mothers and infants at parturition was carried out. Vitamin-B_{12} and P.G.A. levels are lower in the mothers. The role of P.G.A. and vitamin B_{12} in pregnancy is discussed.

We are indebted to Dr. Alan F. Guttmacher, Director of the Department of Obstetrics and Gynecology of Mount Sinai Hospital, and to his staff for generous co-operation. This work has been supported by Grant RG-4446 from U.S. Public Health Service.

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The National Society for Clean Air has recently issued a new edition of the *Clean Air Year Book*. It contains information about the Clean Air Act and related matters, together with general and technical information on the problem of air pollution, and lists of recent papers, publications, and interested organizations. The *Year Book* also includes the Society's annual report for 1957 and information about its organization and activities. The report, discussing the Clean Air Act, is optimistic. "The central government," it says, "has done much to ensure that the Act is in no way neglected," and adds, "How industry as a whole will meet the challenge of the Act remains to be seen." Local authorities, the report continues, are giving considerable attention to their responsibilities under the Act, although the number and size of the smoke control areas so far projected is comparatively small when measured against the annual target proposed by the Beaver Committee. The *Year Book* may be obtained from the Society, Palace Chambers, Bridge Street, London, S.W.1, price 2s. (or 2s. 4d. by post).

ASSESSMENT OF A NEW SIMPLE COLORIMETRIC TEST FOR PROTEINURIA

BY

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AND

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This communication describes the trial of a new test for proteinuria which is based on a principle not previously applied to the analysis of urine. Current tests for proteinuria are turbidimetric, and depend upon the precipitation of the proteins by heat or by various acids; they all have the disadvantage that urine which is already turbid requires filtration or centrifugation before testing.

The new test is colorimetric and may be performed upon turbid urines without filtration. It is based upon the "protein error of indicators" (Clark, 1928; Feigl, 1956). When a solution of protein is added to a *p*H indicator a colour change takes place which is not due to a change in *p*H.

The test material which we have investigated ("albustix") consists of a strip of paper. One end of this strip is impregnated with an inert base containing tetrabromphenol blue (tetrabromphenoltetrabromsulphonphthalein) buffered to *p*H 3 with a citrate buffer. Saturation with a protein solution causes a change in colour, from yellow through green to blue, the amount of colour change varying with the concentration of protein in the solution.

Method

By the addition of normal human serum to normal urine (shown by ultrafiltration to contain about 1.5 mg. of protein/100 ml.) solutions of protein in urine were prepared at the following concentrations: 5, 10, 20, 30, 50, 100, 300, 500, 1,000, and 2,000 mg./100 ml. These protein concentrations were tested in urines at specific gravities of 1005, 1015, and 1025, and at *p*H 5, 6.5, 7.5, and 8.5. The specimens were tested on preparation and after standing at room temperature for 24 hours and 48 hours. We also tested 200 random urine specimens from normal subjects and hospital patients.

All of these specimens were tested by two methods: (1) *Standard salicylsulphonic acid test* (Harrison, 1957): 5 ml. of urine + 0.5 ml. of 25% salicylsulphonic acid. (2) *Albustix*: The whole treated end of the albustix strip was dipped into the urine, and withdrawn as soon as the paper was wet. The colour which developed was compared, after about five seconds, with the colour scale provided, which gives readings of 0, 30, 100, 300, and 1,000 mg./100 ml. The results could be read in daylight or by artificial light, but colour comparison was slightly easier in daylight.

Some specimens of normal urine were tested with albustix both before and after removal of all traces of protein by ultrafiltration.

Specimens of urine containing (1) tolbutamide, and (2) radio-opaque materials—sodium diatrizoate ("hypaque"), sodium acetrizoate ("diaginol"), iopanoic acid ("telepaque"), diodone, iodoxyl ("pylectan"), "biligrafin," "urografin," and "endografin"—were tested. As these substances are known to give false-positive results with the salicylsulphonic acid test, these specimens were also tested by the standard "boiling test" for protein (Harrison, 1957), as well as by albustix and salicylsulphonic acid.

*Employed under a whole-time grant from the Royal Free Hospital Endowment Fund.

To compare the accuracy of albustix and Esbach's method (Harrison, 1957) in quantitative measurement of proteinuria, specimens of urine from a nephrotic patient were used. Serial dilutions of these specimens were made with normal urine. The true protein concentrations in these diluted specimens were calculated from the results obtained by a micro-Kjeldahl assay (Harrison, 1957) performed upon the undiluted specimens. The range of protein concentrations so tested was from 15 to 700 mg./100 ml.

We have not investigated the manufacturers' suggestion that the test can be performed by the patient placing the albustix strip in the urine stream.

Results

A change in colour of the albustix strip was obtained with all specimens of urine which gave positive results with the standard salicylsulphonic acid test for proteinuria (147 specimens). The amount of colour change varied according to the protein concentration, but quantitation was not always reliable. Some normal urines also gave a colour change.

The results obtained with the specimens of urine of known protein content are summarized in the Table. In general, less accurate results were obtained in alkaline specimens of high specific gravity, when albustix often gave a reading greater than the true protein content.

Comparison of Actual Concentrations of Protein in Urine, and Albustix Results

Urine Protein Concentration (mg./100 ml.)	Concentration as Indicated by Albustix (mg./100 ml.)
0	0–less than 30
5	Trace–30
10	Trace–30
20	Trace–30
30	About 30
50	30–100
100	100–300
300	About 300
500	300–1,000
1,000	300–1,000
2,000	300–1,000

As shown in the Table, a proteinuria of 5 mg./100 ml. often gave the same degree of colour change as a proteinuria of 20 mg./100 ml. The lowest protein concentration at which a consistent degree of colour change was obtained was 30 mg./100 ml.

Of 161 random specimens judged to be protein-free by the salicylsulphonic acid test, 44 gave a detectable colour change with albustix. This false-positive colour change was usually slight and patchy, but was occasionally comparable to that obtained with urines known to contain 20 mg. of protein per 100 ml. After ultrafiltration the false-positive results were still obtained.

Little change in the albustix reading was observed when specimens were tested after standing at room temperature for 24 and 48 hours. In no instance did the reading change by one increment on the colour scale.

In comparing the value of Esbach's method and albustix as quantitative tests it was found that albustix gave more accurate results with low protein concentrations. It is known that Esbach's test is especially unreliable in the lower ranges. With higher protein concentrations (above 300 mg./100 ml.) albustix showed no advantage over Esbach's test.

Albustix did not give false-positive results with urine containing tolbutamide and the various radio-opaque materials, which all gave positive results with the salicylsulphonic acid test.

Four specimens of urine from patients with myelomatosis gave positive results with albustix. These specimens contained Bence Jones protein only.

Discussion

The advantages of albustix over the standard protein tests are as follows. The test is simple, is quick to perform, and requires the minimum of apparatus. It is not necessary

to filter urines which are turbid. With albustix a positive result is indicated by a colour change; this is easier to assess than the change in turbidity obtained with the precipitation tests for proteinuria.

It is important to consider the sensitivity of albustix in comparison with other tests for proteinuria. It is generally agreed that normal subjects may excrete up to 50 mg. of protein in 24 hours (Rigas and Heller, 1951). In view of this, Fishberg (1954) has given as an acceptable definition of proteinuria: "When protein is present in urine in amounts sufficient to be detected by ordinary clinical tests which . . . are not sufficiently sensitive to detect normal amounts." The clinical tests for proteinuria (boiling, salicylsulphonic test) are generally accepted as sensitive to 5–10 mg. of protein per 100 ml. of urine when properly performed (King, 1951; Baron and Oakley, 1957; Rice, 1957). If albustix could be shown to detect 5–10 mg. per 100 ml. it would be acceptable as a clinical test for minimal proteinuria.

We have, in fact, found that albustix always gave a colour change with 5 mg. of protein per 100 ml. of urine, although the degree of colour change was often very slight. It may therefore be considered to have the sensitivity required. Unfortunately there was an appreciable proportion of apparent weak false-positive results with albustix. That these were false-positive results and were not due to physiological traces of protein is inferred by the observation that the same change in colour occurred with albustix before and after the removal of all protein by ultrafiltration. (We have not investigated the possible causes of the false-positive results.) A colour-change with albustix indicating less than 30 mg./100 ml. is therefore not specific for protein. If it is required to demonstrate proteinuria of less than 30 mg./100 ml. it is necessary to perform a salicylsulphonic acid or boiling test on urines giving these slight colour changes to verify the presence of protein.

The lowest protein concentration which is designated by the manufacturers on the colour scale is 30 mg./100 ml., and a colour change with albustix indicating a protein concentration of 30 mg./100 ml. or more always means proteinuria.

In the concentrations above 300 mg./100 ml. quantitation is unreliable. We feel that the colour scale should be modified to give four readings: "negative," "trace," "positive," "strong positive." These are respectively equivalent to protein concentrations of 0, approximately 30, approximately 100, and above 300 mg./100 ml.

In contrast to the salicylsulphonic acid test, albustix does not give false-positive results with urines containing radio-opaque materials or tolbutamide. This last fact may make albustix especially useful in diabetic clinics where patients are being treated with tolbutamide.

In view of these observations we make the following recommendations. Albustix is a convenient and reliable test for use by general practitioners, by nurses, and in large clinics when it is inconvenient to perform the boiling or salicylsulphonic acid test with sufficiently critical technique to ensure the highest sensitivity. Albustix provides a satisfactory test if unequivocal demonstration of minimal proteinuria is not required. The standard tests are preferred for laboratory use, except for screening.

In "albutest" the same principle is used in tablet form. An evaluation of this product has been made by Leonards (1957) and Rice (1957), both workers claiming that albutest could detect levels of 20 mg./100 ml.

Summary

A new manufactured colorimetric test for proteinuria, which involves dipping a prepared strip (albustix) into urine, has been investigated. The test is simple and convenient.

Colour changes were always obtained with specimens of urine containing 5 mg. of protein per 100 ml. or more. Slight false-positive colour changes were sometimes given by protein-free urines. Colour changes indicating protein concentrations of 30 mg./100 ml. or more were specific for protein.

The test is roughly quantitative within the range 50–300 mg./100 ml. The clinical applications of this test are discussed.

We thank the Royal Free Hospital Endowment Fund for their support, the Ames Company (London) Limited for supplies of albustix; and Professor N. H. Martin and Dr. A. L. Miller for urines containing Bence Jones protein.

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LABORATORY TRIAL OF A PAPER STRIP TEST FOR PROTEINURIA

BY

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A recent test for proteinuria employs impregnated paper sticks ("albustix") which remain yellow when dipped in normal urine but become green or blue if the urine contains protein. A five-step colour scale is provided, said to correspond to 0, 30, 100, 300, and 1,000 mg. of protein per 100 ml. of urine. The strips contain citrate buffer, *p*H 3 approximately, and an indicator, tetrabromphenol blue (tetrabromphenoltetrabromsulphonphthalein). The test is based on the so-called "protein error of indicators" and is not related in principle to either the heat-coagulation or the sulphosalicylic acid test for urinary protein.

Existing tests for urinary protein, although reliable and sensitive when carefully applied, are inconvenient to use outside the laboratory or consulting-room, particularly if a turbid urine requires filtration before the tests can be applied.

The new test, which requires no apparatus whatever, has obvious advantages in speed and simplicity. Since, however, it is based on an alteration in the effective *p*H range of an indicator, it was thought possible that differing conditions of *p*H, concentration, and buffering capacity of urine might cause some variation in the results of the test. The strips were therefore tested on a number of natural and modified urines in order to assess sensitivity and reproducibility, while normal and protein-containing urines were artificially varied in respect of *p*H and buffering capacity in order to assess the likelihood of errors from these sources.

Sensitivity and Accuracy of Calibration

Twelve protein-containing urines were each diluted with normal urine until they gave apparently negative indications with albustix, and these diluted urines were then tested for

protein by the heat-coagulation and sulphosalicylic acid tests (Harrison, 1957). All gave a faintly positive reaction to both tests, implying that albustix is slightly less sensitive than the conventional tests.

Plasma of known protein content was added to normal urines to give a range of protein concentrations from 0 to 2,000 mg./100 ml., and strips were dipped and compared with the colour scale. Positive reactions, with a continuous gradation of colour from pale green to blue, were obtained over the range of from 30 to 600 mg./100 ml.; at concentrations less than 30 mg./100 ml. some urines gave negative reactions, while with others the test strips became pale green in patches, the remainder of the strip remaining yellow. At concentrations in excess of 600 mg./100 ml., the maximum (blue) colour was obtained. Although the colour gradation was continuous over the intermediate range of protein concentrations, difficulty was found in matching the strips with certainty against any one step on the colour scale, and it appeared more satisfactory to record the results as "negative," "trace," or "positive," without attempting more precise assessment.

A series of albustix strips were dipped into protein-containing urines, and the estimated protein content, as judged by the colour scale, was recorded. The protein content of the urines was also determined by the micro-Kjeldahl procedure. The results are shown in the Table. Although an appreciable discrepancy appeared in the case of urines 2 and 4, the difference is equivalent to one step of the colour scale and is not likely to be clinically significant.

Protein Content (mg./100 ml.)

	Urine No.							
	1	2	3	4	5	6	7	8
By Kjeldahl ..	75	830	350	140	65	145	210	810
,, albustix ..	100	300	300	30	100	100	300	1,000

Reproducibility

Strips were taken at random from five packages, and were dipped simultaneously into urine containing 200 mg. of protein per 100 ml. The colours were compared immediately and again after 2 minutes. No differences between strips were noted, and the colour had not darkened appreciably after 2 minutes.

The effect of variations in the manner of dipping was studied by dipping one-quarter, one-half, and the whole of the impregnated portion of several strips, for periods of 2 seconds, ten seconds, and 2 minutes, into normal and protein-containing urine. Considerable differences were observed. In particular, partial immersion was found to give patchy and erratic results, while total immersion for 2 minutes or more in protein-free urine gave occasional false-positive indications. When strips were quickly and completely dipped, removed at once, and drained by touching against the side of the vessel the colours were uniform and false-positives did not arise. These effects seem to be due to partial or complete elution of the citrate buffer from the strip, thus allowing the indicator to respond to the normal *p*H of the urine.

Effect of Urine *p*H

The indications given by albustix with naturally acid urine, *p*H 5.2, and naturally alkaline urine, *p*H 7.5, to which protein had been added to give a concentration of 200 mg./100 ml., were compared. A similar comparison was made when 30 mg./100 ml. had been added. In each case the alkaline urine gave a more positive indication, but the difference (less than one division of the colour scale) was insignificant.

Urine containing 200 mg. of added protein per 100 ml. was titrated with 5N HCl over the *p*H range from 7.5 to 1.5, as measured by the glass electrode, and the reaction with albustix was noted at steps of 0.5 *p*H unit. The colour progressively lessened with increasing acidity, and became "negative" at *p*H 2.5. The change in colour over the physiological *p*H range (5–7.5 approximately) was negligible, but the addition of acid to urine—for example, as a preservative—will result in false-negative reactions.

Protein-free urine was titrated with ammonium hydroxide in a similar manner over the range from *p*H 5 to 9.5. An apparently positive reaction for protein appeared at *p*H 9.5 in one instance, and at *p*H 9.1 in another—that is, well above the physiological limit of urinary alkalinity.

Stale urine, *p*H 9.2, and having a perceptible odour of ammonia, was centrifuged free of suspended particles. The supernatant contained no protein by the sulphosalicylic acid test, but gave with albustix an indication corresponding to the maximum colour on the scale. When this urine was brought to *p*H 7 by the addition of HCl, a negative reaction was obtained, confirming that the false positive was due to excessive alkalinity.

Effect of Urine Concentration and Buffering Capacity

Although a number of naturally concentrated protein-free urines, with S.G. from 1025 to 1030, gave negative reactions with albustix, it was thought desirable to investigate whether high concentration and high buffering power could combine to give false-positive reactions.

The buffering capacity of protein-free urine was increased by the addition of solid sodium dihydrogen phosphate and disodium hydrogen phosphate, varying the proportions added in order to bring the final *p*H to 5, 6.5, or 7.5. At *p*H 5, urine saturated with sodium phosphate gave a negative reaction with albustix. At *p*H 6.5, saturation with phosphate resulted in a positive indication, but dilution to half-saturation restored a negative reaction. At *p*H 7.5, half saturation with phosphate gave a faint positive result, while the reaction at full saturation was definitely positive.

Saturation of normal urine with urea resulted in a positive reaction equivalent to 100 mg. of protein per 100 ml., presumably due to interaction between urea and the citrate buffer.

The concentrations of phosphate or of urea required to produce these false-positive indications are, of course, considerably in excess of any which could occur naturally. To study the effect of a possible combination of high buffering capacity, high urea concentration, and high natural alkalinity, a synthetic "urine" was prepared containing 2.5% w/v sodium chloride, 5% w/v urea, and 2.5% w/v disodium hydrogen phosphate anhydrous. This solution, *p*H 8.4, gave a just-perceptible positive reaction with albustix, but when brought to a physiological *p*H of 7.5 the reaction became negative. It therefore appears unlikely that extreme levels of physiological concentration and *p*H could give rise to false-positive reactions, and such a fallacy has not so far been encountered in natural urine.

Possible Fallacies

From the nature of the reaction it appeared unlikely that pathological urinary constituents, other than proteins, could give a positive response, and the reactions of the strips were found to be unaffected by the presence of bile salts, glucose, acetone, salicylates, sulphonamides, or iodide. Toluene, used as a preservative, caused some difficulty, in that if the strip became saturated with toluene it became water-repellent and failed to react.

The presence of blood in visible amount gave a positive reaction for protein, but microscopic haematuria did not give a positive reaction.

Freshly passed urines occasionally gave a reaction equivalent to 30 mg./100 ml. or less, which was not obtained after a mucous cloud had settled out. Mucoprotein, as one would expect, gives a positive reaction, and for this reason it appears inadvisable to use the strip by touching it to the urine as it is passed, at least so far as the first few drops of urine are concerned.

Prostatic "threads," and flakes of epithelial debris in female urine, were found to give locally positive reactions if caught on the test strip.

Stability of the Strips

After four hours' exposure in an air oven at 100° C. the strips showed no difference in sensitivity or colour reaction. Exposure to laboratory air for 24 hours produced pale-blue discoloration, apparently due to ammonia; but, surprisingly, such strips reacted normally to urine. Similarly, prior exposure to HCl fumes apparently caused no permanent damage. Brief exposure to steam or dipping in water did not interfere with subsequent indications, although more prolonged steaming, or washing in running water, resulted in subsequent false positives due to removal of the citrate buffer. For the same reason it appears inadvisable to attempt to use a strip to test more than one urine.

Conclusions

Albustix is a simple and speedy test for proteinuria, and, although less sensitive than the present tests for urine protein, it appears to be adequately sensitive for routine use.

Variation of urine acidity or alkalinity within physiological limits does not interfere with the results qualitatively, but it slightly affects the quantitative indication.

Gross alkaline fermentation of urine can lead to spurious positive indications, while the addition of acid or toluene as preservatives can lead to false-negative reactions. Natural variations of urine concentration and buffering capacity are unlikely to be sources of error.

Consistent results are dependent on the impregnated portion of the test-strip being completely immersed and quickly removed from the urine. The strip should not be left in urine for subsequent inspection.

False-positive reactions due to non-protein substances have not so far been encountered.

Semi-quantitative recording of results is not recommended, apart from a rough classification such as "negative," "trace," or "positive."

I am grateful to Dr. C. P. Stewart for suggestions and criticisms, and to Mr. D. H. Vobes, of Ames Company (London) Ltd., for a generous supply of albustix, and for information on its composition and mode of action.

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On the purchase of hospital equipment, the relevant advisory committee of the British Standards Institution writes: "The B.S.I. enjoys the support of the Ministry of Health in encouraging the purchase by hospitals of equipment conforming to British Standards. At the same time, it is the policy of the Ministry to allow Boards of Governors and Management Committees a good deal of autonomy in the selection of the goods they buy. In consequence there are manufacturers who have co-operated in producing British Standards who state that they rarely receive inquiries for equipment complying with them; on the other hand, hospital officials point out from time to time that they have difficulty in obtaining quotations. Undoubtedly this situation is to a large extent created by tradition and conservatism, manufacturers and users alike preferring to continue, in many cases, with the sale and purchase of commodities to which they are accustomed. There is, moreover, a disappointing lack of awareness that most standards provide alternative types or optional features."—*Fourth Report of the Hospital Equipment Standards Advisory Committee* (February, 1958), obtainable free of charge from the British Standards Institution, 2, Park Street, London, W.1.

LICHEN PLANUS OF THE MOUTH

BY

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The purpose of this paper is to draw attention to lichen planus presenting as a disorder of the oral mucous membrane with minimal or no cutaneous eruption. Forty-five cases are described.

It is well recognized that lesions in the mouth can often be demonstrated in cases of cutaneous lichen planus. Samman (1956), in a series of 121 cases, recorded mouth lesions in 77%; and, of 227 cases of lichen planus seen in the United Bristol Hospitals from 1949 to 1956, mouth lesions were present in 51%. However, it does not seem to be generally realized that lichen planus can occur in the mouth without any cutaneous eruption.

Present Series

During the period 1950–7, 45 patients presenting with mouth lichen planus have been seen by us, 19 being referred to the Dental Hospital and the remainder to the dermatological out-patient department. It is difficult to assess the real incidence, since our special interest in the condition may have attracted some cases which otherwise would not have been referred. The distribution of new cases seen during the period 1950–7 was as follows:

1949	..	2	1952	..	5	1955	..	7
1950	..	3	1953	..	4	1956	..	8
1951	..	3	1954	..	8	1957 (first six months)		5

During this period the incidence of cutaneous lichen planus in the same clinical area showed no corresponding rise. Of the cases referred to the dermatological out-patient department, 11 were sent to our colleague, Dr. C. D. Evans, and 15 to one of us (R. P. W.). There is therefore evidence of moderate bias, but, on the other hand, some of the mouth cases may well have been treated by general surgeons, physicians, or dental surgeons, whereas most cases of lichen planus of the skin will be seen at dermatological out-patient departments. Thus for every case presenting in the mouth five or six cases of cutaneous lichen planus have been seen in the same period and clinical area, which gives a rough figure of comparative incidence.

The cases have been followed up at a combined dental and dermatological clinic held monthly. Eight have been observed for over three years; 5 for two to three years; 8 from one to two years; 11 from 3 to 12 months; and 13 on one occasion only. There were 30 females and 15 males. The age distribution was as follows:

3rd decade	..	4 cases	6th decade	..	17 cases
4th "	..	6 "	7th "	..	4 "
5th "	..	13 "	8th "	..	1 "

One patient's mother suffered from typical lichen planus confined to the mouth; it developed nine years after the onset in the daughter.

In six patients the condition was symptomless, the mouth lesions being noticed by the doctor or dentist. Twelve complained of roughness or dryness and two of a metallic taste. Thirty had pain at times which was associated with ulceration. Periods of dysphagia occurred in two patients—in one lesions were not noted on oesophagoscopy and the condition was thought by an E.N.T. surgeon to be globus hystericus, while in the other the symptom coincided with

exacerbations and ulceration of the oral lichen planus. Dentures were worn by 33 patients, but there was no relation between the time of onset and the provision or change of dentures. No association between the extent and distribution of the lesions and smoking habits was noted. Twenty-four patients gave a history of nervous breakdowns, persistent insomnia, or depression, and most patients appeared to be of a nervous sensitive temperament. Seven had had major worries or strain immediately prior to the onset. Four had suffered previously from peptic ulceration.

The areas affected were the inner aspect of the cheek in 34 patients, tongue in 29, lips in 15, gum margins in 8, and palate and fauces in 3. In these areas the commonest sites for the lesions were opposite the occlusal line on the cheek mucosa, on the dorsum and posterior lateral margins of the tongue, and close to but just short of the gum margins. The lesions consisted of discrete or confluent white spots of pinhead size, white streaks, and, less commonly, white patches up to 2 cm. in diameter, which showed spots or streaks at the edges. The white streaks were often curved, sometimes annular or reticular, and in some cases they were present in the buccal sulcus where the edge of dentures impinged. One patient complained of blisters lasting a few hours, but these were never present on examination. Ulceration occurred at times in 30 patients: on the inner aspect of the cheeks in 19; on the tongue in 8 (sides 4, dorsum 3, and ventral surface 1); while in one both cheek and tongue were affected; the gums were ulcerated in one case and lips in another. The ulceration was superficial with a red granular base, although in two cases ulcers on the tongue had a green slough present; they were usually surrounded by white spots or streaks. The ulcers were often opposite a sharp or rough tooth.

The condition completely cleared in only four cases, after 14, 14, and 2 years, and 6 months respectively, and four further cases had minimal relics after 10, 5, 3, and 2 years respectively. If the history and the period of observation are taken together the condition was still present after 10 years in 2 patients; between 5 and 10 years in 5, 3–5 years in 7, and 1–3 years in 15; and under 1 year in 8. When the condition cleared the affected mucosae became normal except on the dorsum of the tongue, where permanent smooth patches usually remained, and at the sites of previous ulceration slight scarring was sometimes apparent.

In one patient an epithelioma developed on the site of recurrent ulceration of the buccal mucosa of 13 years' duration. Five years previous to the epitheliomatous change the patient had received treatment with fractional doses of *x* rays, but it is unlikely that the small dose (300 r at 85 kV) would have played a part in the initiation of the tumour. One other patient with recurrent ulceration of the buccal mucosa of 10 years' duration developed an epithelioma on the lower lip; no lesions had been noticed on the lip by the patient or by us during previous clinical examination, and the epithelioma was said to have occurred on the site of a cigarette burn.

Minor lichen planus lesions were discovered on the skin in six patients at the first visit, while four others developed such lesions during the period of observation. Similarly, three patients showed anal and vulval lichen planus initially, while 3 developed these later. Thus, including 3 patients who gave a history of previous lichen planus of the skin, 19 of the 45 patients seen had other manifestations of lichen planus in addition to the oral lesions. It is of interest that eight patients showed various patterns of minor eczematous eruptions, one had psoriasis, and one had chronic urticaria during the period of observation.

Confirmatory biopsies were carried out in three cases, but those that were clinically atypical have been excluded from the series.

There is no specific treatment of the condition. Explanation and reassurance, simple psychotherapy, and the use of sedatives and other general supportive treatments have been employed. Some cases improved after treatment with arsenic, aneurine hydrochloride, or injections of cyanocobalamin, but when assessing the value of these treatments it is impossible to exclude the effects of suggestion or the natural fluctuations in the course of the disease. It is clearly important to reduce trauma from sharp teeth or rough dentures, particularly in cases with ulceration. The reduction of secondary infection by chlortetracycline mouthwashes every few hours appeared to help in some cases with severe ulceration.

Discussion

Lichen planus presenting in the mouth has been recorded by a number of authors. Trautmann (1911) reported 30 cases of lichen planus affecting the mucous membranes of the mouth, nose, and pharynx, while in a further 19 cases skin involvement followed the oral lesions. Fox (1931) described 10 cases of lichen planus confined to the mouth, and Cooke (1954), in an excellent paper, has reported a series of 50 cases. A general review of lichen planus with an account of the oral manifestations has been recorded by Darling and Crabb (1954, 1955). The clinical appearance is usually so typical that, provided the examiner is aware of the condition, little difficulty is encountered in diagnosis. Plaques of lichen planus may be difficult to differentiate from leucoplakia, but there are nearly always some typical lichen planus papules or streaks in the vicinity. Patches of lupus erythematosus are often bluish red, with occasionally an adherent slough; additional typical lesions elsewhere can usually be relied on to settle the diagnosis. Moniliasis may be distinguished easily by the redness of the intervening mucosa and the ease with which the white spots or patches may be removed. Cooke has pointed out the importance of recognizing the common white streak, running along the buccal mucosa parallel to the occlusal plane of the teeth, which is a functional keratosis.

The development of carcinoma on the site of lichen planus must be very rare, but, in view of the cases in the present series and of reports in the literature (Montgomery and Culver, 1929; Saad, 1931; Miller, 1947; Carteaud and Stiegler, 1950; Périn *et al.*, 1950, 1951; Marshall, 1951), the possibility cannot be excluded.

It is interesting that lichen planus of the mouth shows much the same features as cutaneous lichen planus, modified to some extent by the moist environment and exposure to trauma. The clinical picture of the disease in respect of age, sex, associated emotional disorders, occasional family history, variation in type of lesion, and prolonged intermittent course is in almost every respect the same for both oral and skin lesions.

Summary

Forty-five cases are described presenting with lichen planus in the mouth, having no or minimal cutaneous eruption. The incidence, clinical details, and course are discussed. Ulceration occurred in 30 patients, and 2 developed an epithelioma.

We thank Dr. C. D. Evans for referring so many cases to us, and Professor C. B. Perry for his help in the preparation of this paper.

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Medical Memorandum

A Case of Renal Moniliasis

Recent literature indicates that the successful use of antibiotics against bacterial infections may provide conditions in which the normal commensals, particularly yeasts, become dangerously pathogenic. Whether this is due to direct stimulation or to the eradication of competitors for sustenance is doubtful, but cases have been described of septicaemia with candida in metastatic abscesses in the brain and renal cortex and of fatal pulmonary moniliasis. All of these followed antibiotic treatment for bacterial infections.

In the urinary tract, monilial infection of the bladder gives rise to cystoscopic appearances resembling those of oral thrush with a white curdy membrane (Sauer and Metzner, 1948), but we have been able to find only one paper (Albers, 1953) describing moniliasis of the renal pelvis. Albers reported two cases of unilateral monilial infections of the renal pelvis. Both followed antibiotic treatment of bacterial infection, one associated with calculus and the other following renal colic. In both cases nephrectomy was performed, but this did not effect a complete cure in the second case, which nevertheless became symptom-free.

It is interesting to note that the post-nephrectomy pyuria of the second case not only did not respond to sulphonamides but the drugs seemed to provoke a recrudescence of monilial growth. One of these cases had passed a whitish membrane loaded with candida before operation. In both cases the removed kidneys showed pyelonephritis with leucoplakia in the pelvis.

CASE REPORT

The patient, aged 51, an active wife of a restaurateur, was rather obese. In 1952, having had right renal pain for nine years, she was referred for surgical opinion. An intravenous pyelogram showed a silent right kidney containing calcified shadows; cystoscopy revealed a few tuberculous ulcers in the bladder, and tubercle bacilli were found in the urine. The left kidney was normal. After removal of the right kidney, which was disorganized by tuberculous disease, streptomycin and isoniazid produced a satisfactory result. The bladder became normal, and at no time since have any tubercle bacilli been found in spite of repeated culture and inoculation of guinea-pigs.

After three months at a sanatorium her health in general recovered fully and remained good. She did, however, complain of slight renal pain on the left, but the urine remained sterile and free from pus. An intravenous pyelogram showed rather poor concentration, but the outlines of the pelvis and calices appeared normal. There was some stress incontinence and this was treated by a gynaecologist in May, 1955.

In March, 1956, she sought advice after having become seriously ill over some weeks with left renal pain, low-grade pyrexia, general malaise, and vomiting. The urine contained some pus but was sterile. An intravenous pyelogram still did not concentrate well, so a retrograde pyelogram was carried out. This showed some rather curious filling defects in the pelvis and major calices which at the time were attributed to the presence of air or possibly blood clot. Although a clinical diagnosis of renal tuberculosis was made and appropriate treatment (streptomycin and isoniazid) initiated, no tubercle bacilli were found and symptoms abated. Convalescence was slow.

Three months later there was a recurrence. A catheter specimen then contained pus cells and culture yielded a mixed growth of *Escherichia coli* and candida-like organisms. The coliform organisms were found to be sensitive to oxytetracycline, and this drug was accordingly prescribed; she had provisionally been given chloramphenicol, which was then stopped. Again symptoms receded for a short while, to recur a fortnight later when a catheter specimen produced a pure growth of candida-like organisms. Mycostatin ("nystatin") was then prescribed at 1,000,000 units thrice daily. This rapidly controlled the symptoms but made little difference to the bacteriological findings. In addition, she again suffered increasingly from vomiting, so that she was readmitted to hospital (October 15). She then began to show signs of renal insufficiency: blood urea had risen from 30 to 44 mg./100 ml., and was later to rise to 63 and 75 mg./100 ml. The bladder was normal on cystoscopy, but urine from the left ureter was opalescent and contained small particles. Large numbers of candida-like organisms were found in it, and another retrograde pyelogram showed the same filling defects as before. It seemed likely that this filling defect was due to a "whitish membrane loaded with candida" similar to that passed by Albers's patient.

Attempts were made to wash out the renal pelvis, but with no success, and a little gentian violet was injected. This was a rather unfortunate procedure, as it made her quite ill for a few days, and a repeated straight *x*-ray film showed definite calcification of the "filling defect" in the renal pelvis. Pyelotomy was then decided upon. The pelvis was opened with some difficulty owing to the hypertrophy and perinephritis. The "calculi" consisted of a soft whitish mud. As much as possible was removed and the pelvis washed out. This mud was found to consist of a structureless debris, some calcareous deposits, and vast numbers of candida. The patient was not much upset by the operation, and her urinary output remained satisfactory.

A few days later the pelvis was washed out again with solution G, a solution of magnesium citrate (Kayser's solution). This procedure was unfortunate, too, as it apparently resulted in blockage of the ureter by some of the debris. Happily her urinary output was unimpeded by this, as she developed a leak through the lumbar incision. Some days later the ureter was easily catheterized and the pelvis washed out with solution G. This was repeated several times with solution G and 1:10,000 merthiolate, and throughout the urinary output was maintained either through the lumbar wound or per vias naturales, and eventually the wound healed completely. Convalescence proceeded slowly, mainly under cover of a prolonged course of mycostatin. The blood urea level fell gradually to 45 mg./100 ml. and later to 39 mg./100 ml. On January 8, 1957, she passed a small "stone" consisting chiefly of protein with a small amount of ammonium urate: no nucleus and no candida.

At the time of writing she had only minimal symptoms, and a catheter specimen showed a few pus cells and *Staphylococcus albus* only. An intravenous pyelogram showed a filling defect in the lower half of the pelvis only and none in the calices. Concentration was good. No further treatment was contemplated at the time unless the symptoms underwent exacerbation.

A culture of the urine was sent to Dr. C. F. Barwell, of the London Hospital, who agreed that the organisms belonged to the genus *Candida*, but said that they were not *C. albicans*.

It is suggested that the finding of candida in infected urine should lead to the administration of mycostatin as well as the antibiotic appropriate to the bacterial infection.

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Reviews

CHRONIC BRONCHITIS

Recent Trends in Chronic Bronchitis. Edited by Neville C. Oswald, T.D., M.D.(Cantab.), F.R.C.P.(Lond.). (Pp. 199+vii; illustrated, 30s.) London: Lloyd-Luke (Medical Books) Ltd. 1958.

Chronic Bronchitis Emphysema and Cor Pulmonale. By G. H. Stuart-Harris, M.D.(Lond.), F.R.C.P., and T. Hanley, M.D.(Lond.), M.R.C.P. In collaboration with Marjorie Clifton, M.D.(Sheffield), Margaret M. Platts, M.D., B.Sc. (Sheffield), M.R.C.P., J. D. S. Hammond, M.B., Ch.B. (Sheffield), M.R.C.P., and W. Whitaker, M.D.(Leeds), M.R.C.P. (Pp. 252+v; illustrated. 42s.) Bristol: John Wright and Sons Ltd. 1957.

The almost simultaneous publication of two books on chronic bronchitis, each based on the experience of an active group of investigators, is an index of the long-overdue interest which is being taken in this important cause of disability and death. One is based largely upon work done in the Bronchitis Clinic, Brompton Hospital, London. In it Dr. Oswald deals with clinical aspects of chronic bronchitis, Dr. Lynne Reid with pathology, Dr. George Simon with radiology, and Dr. J. R. May with bacteriology. Chapters on the cardiac aspects by Dr. R. V. Gibson, on air pollution by Dr. P. J. Lawther, and on the disturbance of respiratory function by Dr. D. V. Bates constitute admirable but somewhat independent essays on these subjects. The book ends with a useful chapter on aspects of bronchitis in general practice by Dr. John Horder. The other book is based upon work done in the Department of Medicine of the University of Sheffield, under the general direction of Professor Stuart-Harris. The responsibility for individual sections is not stated. Professor Stuart-Harris and Dr. T. Hanley are named as the principal authors, and Dr. Marjorie Clifton, Dr. Margaret Platts, Dr. J. D. S. Hammond, and Dr. W. Whitaker as having collaborated in the writing of the book.

The two books present interesting similarities and differences. This is not surprising, since the workers in the two centres from which they come have adopted approaches to the problems of investigating chronic bronchitis which most fortunately have differed in emphasis. The difficult problem of the definition of chronic bronchitis is tackled in interestingly different ways in the two books. Dr. Oswald falls back upon a historic survey of the use of the term "bronchitis" and of the development of medical opinion concerning the malady to which it is applied. Professor Stuart-Harris describes a field survey of the incidence of certain symptoms in order to discover whether any combination of them can be devised to provide a convenient and useful definition of chronic bronchitis. The Brompton workers have made their most important contributions in the fields of morbid anatomy, radiology, and bacteriology, and in clinical description; whereas the original contributions of the Sheffield workers have been in the field of epidemiology, especially in industry, and in careful clinical and physiological studies of the terminal stages of the disease with its cardiac effects. The two books are therefore to a large extent complementary, although they cover the same general field. While emphasizing the incompleteness of existing knowledge, they provide useful summaries of what is known, of current opinions, and of work in progress. Both should be read by all those interested in any of the many aspects of this common disease.

J. G. SCADDING.

ARTIFICIAL LIMBS

Artificial Limbs. By Leon Gillis, M.B.E., M.B., B.Ch., M.Ch.Orth., F.R.C.S. Foreword by Sir Harry Platt, LL.D., M.D., M.S., F.R.C.S., F.A.C.S.(Hon.). (Pp. 449+xiv; illustrated. £15.) London: Pitman Medical Publishing Co., Ltd. 1957.

Artificial Limbs follows an equally large book, *Amputations*, published in 1954. The author's long and unique experience on the staff of Queen Mary's Hospital, Roehampton, and his contact with the limb-fitting service and limb manufacturers have enabled him to produce a most comprehensive book. He describes the artificial means of replacing a limb and the principles of limb fitting. It is made clear what should be the aims of the surgeon and what the manufacturer can do, but less stress is laid on the requirements of the amputee and how he can get these. The book is scientific as well as practical, and in its narrow field is a contribution to the national effort to help humanity. Throughout the book the reader will appreciate the author's idea that there is room for improvement in the principles of limb design.

There is little doubt that a surgeon or fitter who has never been to a limb-fitting centre will find the book less helpful than one who knows the work there, but those working in centres throughout the world will find what is not written elsewhere. There is a tendency to lay stress on the unusual, and the description and illustrations of the requirements of double amputees are somewhat excessive. On some subjects patients and surgeons will consider views expressed somewhat optimistic—for example, the value of a tilting table subsequent to a hind-quarter amputation. Manufacturers and fitters should study this book, disregarding the high price. It is unusual for a companion volume to be published by a different house from that of its elder brother, and the reader who is interested in the subject-matter of both the volumes may consider that repetition could have been avoided and many illustrations omitted if this had been presented in a single volume.

ST. J. D. BUXTON.

PSYCHOTROPIC DRUGS

Psychotropic Drugs. Edited by S. Garattini and V. Ghetti. (Pp. 606+xiv; illustrated. 95s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. London: Cleaver-Hume Press, Ltd. 1958.

Few can have any idea of the volume of work which is being done on the pharmacology of the brain, and those who are anxious to find out can study this book of over 600 pages, which contains contributions from 97 groups of workers from all over the world. Some of it is fascinating. Thus workers in Los Angeles have discovered that it is possible to implant electrodes in different points of the brain of the rat and to connect them up in such a way that when the rat is put in a cage where there is a tapping key it stimulates its own brain by pressing the key. The current which passes is small, being measured in microamps, and when the current is raised up to 20 or 30 microamps the rat enjoys the stimulation and presses the key even more and more often during an eight-minute period as the current strength rises. The workers then test drugs on the rat's behaviour. When the electrodes were in one position in the hypothalamus chlorpromazine (2 mg. per kg.) had no effect on the frequency of self-stimulation, but when they were in a different position chlorpromazine abolished the self-stimulation. It is to be said that the evidence of the effect of the drugs seems open to criticism, but the method of testing may fairly be described as intriguing. What kind of sensation does the rat receive?

Many workers have followed changes in the electroencephalogram, which in the drowsy animal shows large waves due to the synchronization of small waves from many parts of the brain. If the animal receives a sensory stimulus this synchronization is arrested and the large waves are replaced by many small ones. It is as if the record of a normal heart-beat was replaced by a record of fibrillation. Drugs which affect this "desynchronization" have then been studied. For the most part the results appear to be no more than a mass of data incapable of interpretation. However, the attack on the problem is on so wide a scale that someone is bound to discover something before long.

J. H. BURN.

CLINICAL RHEUMATOLOGY

Klinische Rheumatologie: Pathogenese, Symptomatologie, Diagnostik und Therapie der Rheumaerkrankungen. By Werner Moll. Foreword by Dr. S. de Sèze. (Pp. 454+xii; illustrated. Sw. Fr. 79.) Basle, New York: S. Karger. 1957.

This book on clinical rheumatology is bigger than it sounds, since approximately half the text is printed in very small type. Such a device for making a large book seem of reasonable size does not make it more readable. After struggling through the small print one can find a substantial amount of information laid out in a very systematic manner, but it is not especially up to date. For example, in discussing the treatment of gout, "benemid" (probenecid) is dismissed in nine lines as a new American remedy, and the important uricosuric analogues of phenylbutazone are not mentioned; and in the chapter on rheumatoid arthritis the rheumatoid serum factor gets one page of small print. At the back of the book there are 166 illustrations, but nearly half of these consist of photographs and radiographs of the hands of patients with early rheumatoid arthritis, which all look alike, and there is no indication that the author has been selective in the material he presents. For those who read German with ease the most informative chapter is probably the one on disk disorders.

J. H. KELLGREN.

DIGITALIS

Digitalis. Compiled and edited by E. Grey Dimond, M.D. (Pp. 255+xiv; illustrated. 52s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This book reports the proceedings of a conference on digitalis held at the University of Kansas Medical School. The contributions range over a wide field, and the book concludes with a verbatim account of a panel discussion in which the major contributors took part. Many of the papers repeat information which is readily available elsewhere, but some break new ground. Thus the fate of digitoxin has been studied by Friedman using a sensitive method of assay on the embryonic duck heart, and also by Okita using radioactive digitoxin. The results are in good agreement, and refute the previously accepted view that this glycoside is selectively concentrated in cardiac tissue and is stored in the extravascular fluid. Lown, in an interesting article dealing with the relationship between digitalis and potassium, produces good evidence that diuresis may potentiate the effect of digitalis by producing potassium depletion. Intravenous calcium is said to be of value in restoring normal rhythm to the digitalized heart during cardiac operations. Pharmacologists and cardiologists will find much to interest them in this book. Many important aspects of digitalis therapy—as, for example, its relationship to treatment by quinidine—are, however, not mentioned, and it by no means gives a comprehensive account of the drug. Nevertheless, it is stimulating to read about the advances made by specialists in this field, and it is great tribute to the importance of digitalis as a remedy that it can continue to occupy the attention of both pharmacologists and clinicians nearly 200 years after Withering's dramatic discovery.

E. J. WAYNE.

HYPOPHYSECTOMY

Hypophysectomy. Edited by O. H. Pearson, M.D., F.A.C.P. (Pp. 154+xi. 37s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This monograph contains some 16 papers on various aspects of hypophysectomy, which were delivered at the Sloan Kettering Institute in New York in March, 1956, together with the subsequent discussions from the floor. With the exception of one paper on surgical hypophysectomy in diabetes, the various papers are all concerned mainly with pituitary ablation or destruction in metastatic breast cancer, there being general agreement that the procedure is of little value in other malignant conditions. The four opening papers deal with the techniques and early results of surgical removal, and as they all favour the frontal approach there is inevitably some recapitulation. The concluding papers deal with destruction of the pituitary by radiation using methods ranging from the intrasellar implantation of radon and yttrium[90] seeds to the use of the betatron-produced electron beam. The intermediate papers are concerned with the various endocrine and biochemical changes that follow pituitary destruction and with problems of endocrine replacement. The individual papers are all short, the number of cases with which each is concerned is small, and the follow-up period rarely exceeds two years. Consequently the various observations and conclusions arrived at are only tentative. It is interesting that none of the participants appear to have evolved a method which guarantees complete pituitary destruction, either by surgery or by radiation, while several of them concede that a remission of the malignant tissue can occur even although the pituitary destruction is incomplete. Again, there seems to be no single endocrine or biochemical test which post-operatively can indicate with absolute confidence that the pituitary has been completely destroyed. For these reasons, while the monograph will be of interest to those directly engaged in the treatment of intractable breast cancer or in studying pituitary dysfunction, it must be regarded as a progress report rather than an authoritative survey.

MURRAY A. FALCONER.

THE ACUTE ABDOMEN

The Early Diagnosis of the Acute Abdomen. By Sir Zachary Cope, B.A., M.D., M.S.(Lond.), F.R.C.S.(Eng.). Eleventh edition. (Pp. 188; illustrated. 18s.) London, New York, Toronto: Oxford University Press. 1957.

The eleventh edition of Sir Zachary Cope's clinical treatise is a worthy successor to its predecessors. The whole book has been revised and there are several important additions. Dissecting aneurysm and leaking aneurysms are now included, and jejunal diverticulitis and volvulus of the stomach make a new appearance too. The special problem of the acute abdomen in the tropics is well covered, and a new and original chapter is included to assist the general practitioner to come to a precise diagnosis when faced with a case of acute abdominal disease. In this chapter there are a number of very helpful practical hints. It is perhaps carping to mention that the acute abdominal presentations of polyarteritis nodosa and of porphyria, sometimes very puzzling, are not included.

IAN AIRD.

The two hundred and fiftieth anniversary of the birth of Linnaeus was commemorated in Haarlem on May 23, 1957, and the addresses delivered on that occasion have now been published as Communication No. 103 from the National Museum for the History of Science, Leyden. They comprise a welcoming speech by Professor H. J. Lam; "Linnaeus in Holland," by Professor H. Engel; "Linnaeus and Medicine," by Professor G. A. Lindeboom; and an epilogue by Professor Lam.

An account of the *National Voluntary Health Associations in Canada* has been published by the Health League of Canada (111, Avenue Road, Toronto). It summarizes their objectives, their existing organization, and how they are financed. Professional organizations are excluded, but a report is included from each voluntary association having as its objective the attack on some particular disease or group of diseases.

The *B B C Handbook 1958* contains information on the administration of the Corporation, its history and publications. Statistics are provided from listener-research reports on both sound and television programmes. There are notes on programmes sent out to both home and overseas listeners. Members of the special advisory councils and committees are listed and details of last year's balance sheet are given. This useful reference book can be obtained from the British Broadcasting Corporation, London, W.1, price 5s.

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OPEN FOR INSPECTION

It is not often that the mind of the civil servant is laid open for inspection. So that the medical profession may have a better idea than hitherto of the views of the Treasury and the Ministry of Health about the payment of doctors in the N.H.S., we are publishing a full report in the *Supplement* of this week and next week of last week's cross-examination by the Royal Commission of our joint employers—the Treasury and the Ministry of Health. There is a complete deadlock between those representing the medical and dental professions and the Ministry of Health on the interpretation of Spens. Sir John Hawton said it was always the Government's view that Spens applied only at the moment of entry of the profession into the National Health Service, and that the primary consideration now was the level of remuneration received by members of comparable professions. "We cannot accept this apparent theory," Sir John said, "that there is some mystique about Spens for all time." He could not accept that "a particular document should be an absolutely sacrosanct yardstick by which the thing is automatically adjusted." He referred to the profession's view that the Spens Report was fundamental to its continued remuneration in the N.H.S. as "this extreme doctrine." Pressed by members of the Commission, he said that what he was trying to say was that there was "nothing unique about the situation of these professions." And when asked if it was his view that the B.M.A. interpretation was a travesty, Sir John Hawton replied, "Yes, I think it is completely unwarranted. If it was universally applied to other professions and other occupations, it would be an impossible situation." The Commission's Chairman, Sir Harry Pilkington, pointed out that it was not only the B.M.A. that had this view, but also those who represented the consultants and the dentists, and other members of the Commission drew attention to passages in Spens which would justify the profession in its view that the Spens Reports had distinct reference to the future, and to the letter from the Ministry of Health on May 2, 1950, which stated, "the Minister agrees that the Spens Report remains the basis of the remuneration of general medical practitioners until such time as after the usual consultations some other basis is substituted." Sir John Hawton seemed so desperately anxious to prove that there was nothing unusual about the position of the medical profession, nothing that differentiated them from other professions to justify any kind of treatment he would regard as exceptional, that we fear he must have entirely forgotten one simple fact—namely, that in 1948, ten years ago, it decided to surrender a large measure of its freedom as an independent profession by accepting service in the State-provided N.H.S. on the terms of the Spens Reports.

Although the leader of the Treasury team, Sir Thomas Padmore, said they were happily appearing in quite a secondary role, any illusions the hearer might have had on this diminished as the two-day hearing proceeded. Sir Harry Pilkington asked him whether he could think of any other profession in which there had been no change in remuneration between 1951 and 1957. Sir Thomas could think of no other group which had stood still during that period, but showed how much he agreed with Sir John Hawton when he said that one had to take into account the size of the change made in 1951 as a result of the Danckwerts Award. In other words, the Treasury and the Ministry of Health, though they had to accept the Danckwerts Award, showed their disapproval of its size—and for that matter of its terms of reference—by refusing to undertake any step to readjust doctors' remuneration during those six years. Sir Harry Pilkington hoped that the Government would not use the medical profession as a regulator of salaries, but would regard the profession's claims on their merits. And Sir Thomas Padmore replied that the merits of the profession's claim would be examined "in exactly the same way as that of any other employee of the Government or the public service." But when the point was pressed that the Government had turned down the profession's claim in the first instance because of economic circumstances, Sir Thomas said that "all experience goes to show that from time to time, for limited periods, it may well be necessary for the Government to impose on or to require from the whole of the public service certain restraints in regard to remuneration." This period of short-term restriction, according to him, was roughly from the early summer of 1956. And yet, as Professor Jewkes pointed out, in 1956 salaries rose by £300 millions and wages by £564 millions. Was it not possible, therefore, that the doctors would say, "Why should we bear the main brunt of the anti-inflationary policy because our wages are clamped down, particularly if the policy does not succeed"? Sir Thomas's rejoinder was that as the policy did not

wholly succeed the freeze unfroze itself. And when he was pressed again on this point of the doctors and dentists being held back, he replied, "It is one of the disadvantages of being a member of a public service."

We have picked out for comment one or two points from the important evidence given at a public hearing by civil servants of the Treasury and the Ministry of Health. We would urge every doctor to read the accounts in this week's and next week's *Supplement*, because thereby they will gain some insight at least into the workings of the civil service mind. These men are our employers, and have justification in feeling this to be so. They look upon doctors in the Health Service as, in fact, subordinate civil servants not sufficiently under control. For example, although it was admitted that the distribution of incomes among general practitioners would probably turn out to be not so very different from the kind of distribution recommended in the Spens Report, what sounded almost like a complaint was made that it could not be exact because the capitation method of payment did not afford the Ministry a sufficient degree of control: clearly the only control that would comfort the Ministry of Health would be a salaried service. It is no wonder that there have been and are such deep misunderstandings between the profession and the Ministry of Health, and no wonder that this prolonged crisis over pay has been so widely interpreted by the profession as a crisis of confidence.

DANGER ON THE FARM

From April until September chemicals for the control of insects, fungi, weeds, and other pests are being applied to growing crops on our farms. Most of these chemicals are virtually harmless to people who handle them even with the minimum of safety precautions. But a few are dangerous, and it is not always easy to persuade men to handle materials, rather similar in general appearance and method of application, with great care only on special occasions. Experience of accidents in Great Britain over the past ten years is limited to very few fatal or serious cases of poisoning, but the greatest potential danger is during the peak spraying periods of the dinitrocresol (D.N.C.) and chemically related weed killers and some of the organophosphorus insecticides in May and June. The usual cause of accidental poisoning by pesticides is contamination by spills and splashes of the concentrated materials. This may result from bad technique, inadequate training, or faulty equipment. In addition, the workers may be in a hurry to apply the chemical in an emergency or tired after long hours of work during the midsummer daylight.

Accidental poisoning from pesticides is uncommon, and the good record of British agriculture stems from a voluntary control of hazards which is based on advice from the National Agricultural Advisory Services. The advice is supported by the manufacturers and sellers of pesticides, and legislation also provides for the control of the more dangerous materials. For the past two years a voluntary notification scheme has been in operation whereby manufacturers give advance information to an advisory committee of the Ministry of Agriculture, with outside expert members, of their proposals for the use of new materials or of new uses for old materials.[1] Recommendations for the safe use of these materials are made and so far have been accepted by industry. Thus all the advice on labels and explanatory leaflets accompanying the reputable pesticide products are drawn up in conformity with the recommendation of this official committee. Manufacturers are trying to produce less toxic materials—especially among the organophosphorus insecticides—so that they can be applied without the need for elaborate safety precautions, but there is still a place for more toxic ones, because they may be so efficient that fewer applications are needed.

When called to see a patient suspected of suffering from pesticide poisoning, the doctor would be well advised to get the container of the substance his patient may have handled and read the label or leaflets with it. He can then find out whether or not careful precautions are needed for that particular product, and, if so, whether his patient appears to have observed them. A careful occupational history may be an important part of diagnosis, for the early signs of poisoning may be difficult to distinguish from an ordinary illness such as gastro-enteritis or simple exhaustion. If a serious case is encountered, it might be advisable to inquire about any other men working with the victim. Though all the pesticides in use to-day can be applied safely if the recommended precautions are observed, the difficulties of supervision and the enforcement of wearing the proper protective clothing is very difficult.

The dinitrocresol weedkillers have the worst record in Great Britain, and though fatalities have not been recorded in recent years there is reason to suspect that in very hot weather at the height of the season cases might still ocur. The victims have often complained of thirst, excessive sweating, headache, and fatigue before they stop work. Signs of poisoning then develop rapidly, with prostration and collapse. The yellow-stained hands should rouse suspicions

[1] Miller, E. J., *N.A.A.S. Quarterly Review*, No. 36, 1957.
[2] Edson, E. F., *World Crops*, February, 1958.
[3] Kiraki, K., Namba, J., Yamada, M., Fukuhara, A., Kuroda, Y., and Kimura, K., *Jap. med. J.*, 1956, **10**, 1702.
[4] Karlog, O., Nimb, M., and Poulsen, E., *Ugeskr. Læg.*, 1958, **120**, 177.
[5] Quinbey, G. E., and Lemmon, A. B., *J. Amer. med. Ass.*, 1958, **166**, 740.

immediately, and a rapid pulse and respiration with a hot skin should clinch the diagnosis. There is no specific treatment except complete rest and fluids. Barbiturates should be avoided.

The organophosphorus insecticides range from the virtually non-toxic malathion through the moderately poisonous materials like diazinon and demeton-methyl ("metasystox") to the potentially dangerous ones like parathion and the newly introduced "phosdrin" and amiton ("tetram"). The early signs of poisoning are headache, sweating, and abdominal discomfort, and, later, muscular twitching especially round the face. The symptoms may not appear until after work has finished. The diagnosis can be established by a blood-cholinesterase examination. Some hospitals in agricultural areas have experience with this test, and a convenient field kit has been devised which might be available to pathologists willing to visit possible victims.[2] Therapy is by the repeated administration of atropine in doses of 1/50–1/20 gr. (1.3–3 mg.) by injection. Recently chemicals that will reverse the poisonous effects of these organophosphorus insecticides have been discovered and used successfully on animals. Reports of the use of one of them, pyridine aldoxime methiodide (P.A.M.), in men poisoned by parathion have come from Japan[3] and Denmark.[4] No specific recommendations for the correct administration of P.A.M. are as yet available, but we understand that the Chemical Defence Experimental Establishment is at present working on this problem. In any case atropine must accompany the use of P.A.M., so that its administration should never be delayed. Late sequelae from parathion poisoning have not been reported among over 50 cases recorded in recent years from the Continent. The solitary instance of neuritis after parathion poisoning recorded in Germany in 1951 was probably a coincidental illness. It would be helpful if the Ministry of Agriculture inspectors under the Act regulating dangerous pesticides could be told of any suspected case of parathion poisoning so that they can take steps to prevent this in other workers.

A lesser danger exists in handling crops that have recently been sprayed with toxic insecticides. A report from the U.S.A.[5] recounts several incidents in which groups of workers developed mild symptoms of poisoning while pruning and stripping fruit crops recently sprayed with parathion. The authors were convinced that absorption of the parathion was through the skin and not by the inhalation of vapour arising from the sprayed vegetation. The use of arsenic to kill potato haulms has increased; this poison is worth bearing in mind as a possible cause of irritation of the eye, skin, or gastro-intestinal tract among farm workers in the autumn. Antibiotics such as streptomycin are in use on a limited scale to prevent bacterial diseases of plants and trees and might be responsible for an occasional case of hypersensitive reaction. Mercury compounds are still widely applied as fungicides in spite of misgivings about the dangers from residues in food crops. Ethyl mercury salts, popular among tomato growers, are now scheduled poisons as the result of a single fatality attributed to the handling of the concentrated material by a foreman greenhouse worker. It is also worth bearing in mind that there may be some very poisonous materials lying about farms at this time of the year and the possibilities of accidents to children should not be forgotten.

CHLOROTHIAZIDE

The search continues for an oral diuretic which is as effective in controlling oedema as the organic mercurials. Last year we commented[1] on the favourable reports of an aromatic sulphonamide derivative, chlorothiazide, and we publish this week two papers in which the value of the drug is assessed. Chlorothiazide produces a diuresis in man by increasing the excretion of chloride, which is accompanied by an equivalent amount of sodium. In this respect it resembles the organic mercurials, but there is one important practical difference: it causes a much greater degree of potassium excretion. In addition it has the properties of a weak carbonic anhydrase inhibitor, causing an increase in urinary *p*H and bicarbonate, at least initially.[2] The diuretic effect lasts up to 12 hours, and it is sufficient to give 1–2 g. daily by mouth in divided doses.

The few published reports have so far been largely concerned with the use of chlorothiazide in congestive cardiac failure. The number of patients treated has been small, and the period of observation necessarily limited, but nevertheless the results are impressive. A short-term study of this kind is reported on p. 967 by Dr. D. Wynne Davies and Dr. Byron Evans, who have compared the effect of chlorothiazide with organic mercurials in 17 patients suffering from cardiac failure. The authors have been careful to avoid bias in favour of one or other treatment, and their observations show clearly that the new drug is quite as effective as parenteral diuretics, and is moreover free from toxicity. On the other hand, the paper by Drs. A. E. Read, R. M. Haslam, J. Laidlaw, and Sheila Sherlock, from Hammersmith Hospital, suggests that chlorothiazide may have certain disadvantages (p. 963). They have used the drug to treat fluid retention due to portal cirrhosis, and, although a satisfactory diuresis occurred in a high proportion of the patients, this was offset by the frequent occurrence of hypokalaemia and impending hepatic coma. As others have noted, no symptoms resulted from the hypokalaemia, but this is a potentially dangerous

[1] *Brit. med. J.*, 1957, **2**, 1355.
[2] Slater, J. D. H., and Nabarro, J. D. N., *Lancet*, 1958, **1**, 124.
[3] Harington, M., and Kincaid-Smith, P., ibid., 1958, **1**, 403.

complication, and, as the authors stress, is not always corrected by giving up to 6 g. of potassium chloride a day, which is as much as the average person can tolerate. Routine electrolyte determinations should therefore be carried out when prolonged maintenance therapy is required, and it is wise to restrict treatment to only three or four days during the week. Possibly the hypokalaemia is responsible for the tendency to hepatic coma in patients with cirrhosis, but other factors may be involved. A point to be borne in mind when treating cardiac failure is that the action of digitalis is potentiated by potassium deficiency. A further interesting feature of chlorothiazide is that it enhances the action of hypotensive drugs,[3] and may thus be of particular value in the management of hypertensive cardiac failure.

It seems unlikely that this new diuretic will replace the time-honoured organic mercurials, but it may well have a place as a powerful alternative, especially in patients who are refractory or sensitive to the latter. More information is needed about the effects of giving it over long periods. At the present time, 2 g. chlorothiazide costs 7s. 6d., while 2 ml. mersalyl costs only a few pence, though no one will deny the advantage of oral therapy both to the patient and to the hard-working district nurse.

ERRORS IN DIAGNOSIS OF CARDIAC INFARCTION

The electrocardiograph is an essential tool for the accurate diagnosis of myocardial infarction, and, since myocardial infarction is a common mode of sudden death, a wide margin of error may be expected in diagnosis when it has to be made without the aid of a full electrocardiogram. B. C. Paton[1] has recently emphasized the rather low degree of accuracy in clinical diagnosis of myocardial infarction, in a review of 266 necropsies of patients dying from this cause at the Royal Infirmary in Edinburgh. He found that the accuracy rate was only 44%, taking into account both patients who were incorrectly diagnosed as having myocardial infarction and those in whom infarction was found unexpectedly at necropsy.

Most of the diagnostic errors occurred in patients dying suddenly, in whom an electrocardiogram had not been obtained. Silent painless myocardial infarction[2] was another reason for overlooking the diagnosis. The commonest condition confused with myocardial infarction was pulmonary embolus. Another cause of death in the series was gross coronary sclerosis, without evidence of infarction by either injection or serial slicing techniques. However, it is probably undesirable to separate this group of patients too rigidly from those dying of myocardial infarction, since both groups should be regarded as dying of ischaemic heart disease. Other cardiac conditions confused with infarction were congestive heart failure with pulmonary oedema, ruptured or dissecting aortic aneurysm, and pericarditis, each of which may mimic closely myocardial infarction. Pulmonary infection, cerebral haemorrhage, and shock from bleeding after operation all caused difficulty in diagnosis sometimes, and of these post-operative shock from bleeding may be particularly confusing, especially if the infarct is painless.[3]

In contrast to the low rate of diagnostic accuracy in the group as a whole, a high degree of accuracy was obtained in the group with recent infarction, in whom an electrocardiogram had been obtained. Only six incorrect diagnoses were made on the electrocardiogram in 97 cases. These inaccuracies were a matter of detail only. In three patients myocardial ischaemia rather than frank infarction was diagnosed, while in the remaining three left bundle branch block obscured the electrocardiographic picture, though this pattern is in itself pathological and indicative of heart disease.

This study serves to emphasize once again the indispensability of the electrocardiogram for the accurate diagnosis of myocardial infarction. When death is sudden, it should be recognized that a presumptive diagnosis of myocardial infarction is just as likely to be wrong as right, though if there is a previous history of coronary artery disease myocardial infarction is the most probable mode of death. Special care is worth taking in the post-operative period, especially during a phase of hypotension, to recognize myocardial infarction, which may be painless. Similarly, unexplained heart failure, particularly in the elderly, and also hypertension, atrial fibrillation, or Stokes–Adams disease may mask the diagnosis of myocardial infarction.[4] Finally, it goes without saying that no clinical diagnosis of myocardial infarction should ever be considered sufficient without the confirmation of an electrocardiogram, however "classical" the symptoms may appear to be.

[1] Paton, B. C., *Amer. J. Med.*, 1957, **23**, 761.
[2] Parkinson, J., and Bedford, D. E., *Lancet*, 1928, **1**, 4.
[3] Jacobs, T. P., *Ann. intern. Med.*, 1951, **34**, 114.
[4] Evans, W., and Sutton, G. C., *Brit. Heart J.*, 1956, **18**, 259.

MOTHER AND CHILD

To demonstrate statistically what having a good mother means for a child is not the easiest of tasks, but a report[1] published last week is full of interesting factual information on this very point. The authors of the report, Dr. J. W. B. Douglas and Miss J. M. Blomfield, record the results of a national survey made by a joint committee of the Institute of Child Health (University of London), the Society of Medical Officers of Health, and the Population Investigation Committee. The work is an offshoot of the inquiry[2] into pregnancy and childbirth carried out some 12 years ago, when nearly 14,000 women who bore children during a specified week in 1946 were asked detailed questions about their personal circumstances and experiences. The present report, entitled *Children Under Five*, is concerned with the first five years of life of over 5,000 of the children born at the time of the 1946 inquiry. These children are still being followed, but *Children Under Five* takes their story only up to 1951. They come from all parts of Great Britain and from all social classes, and the study, in the authors' own words, "has provided a unique

[1] Douglas, J. W. B., and Blomfield, J. M., *Children Under Five*, 1958, George Allen and Unwin Ltd., London. Price 21s. net.
[2] *Maternity in Great Britain*, 1948, London.

opportunity to describe the home environments in which young children are being brought up and to throw light on a number of problems concerning their health and growth during the pre-school period."

Social changes, as reflected in the histories of the families included in this survey, were for the better during the years under review. The proportion of prosperous families increased, and there was a steady fall in overcrowding. In general, the families of the black-coated workers (a group coming between salaried workers and skilled manual workers) have shown the greatest social improvement: they also had the best record of attendances at child welfare centres. The proportion of efficient mothers fell steeply with decreasing social status, increasing family size, and, in the poorer groups, with increasing numbers of small children. The differences in the proportion of efficient mothers in the various social groups were greatest when the home conditions were poor. In the middle range of families the mother's care is of special importance to the child's growth, because careful planning of expenditure is necessary if the child's nutritional needs are to be met. "For those [families] with the lowest incomes—perhaps a quarter of all—no amount of careful planning can compensate for the inadequate income." As judged by height, girls were more sensitive to a poor environment than boys.

One of the most important findings of the survey was that social class differences in mortality were not so much a reflection of differences in the incidence of disease as of differences in its course. The only illnesses showing a definite increase as housing conditions grew worse were the lower respiratory infections. Surprisingly, accidents occurred no more frequently in the worst homes. The authors go on to say: "The incidence and severity of both illness and accidents was more closely related to the standard of maternal care than to home conditions, and since there were large social group differences in the quality of maternal care we feel that this factor accounts for much of the excess of serious illness and death among the poorer children."

Among other subjects on which this report is highly informative are broken homes, separation of mother from child, working mothers, toilet training, bed-wetting, premature children, and use of maternity and child welfare services. On the last of these topics the authors have something to say which should encourage medical officers of health, for in their opinion "the social and educational approach is still of primary importance in the saving of infant life."

MENTAL ILLNESS AND CHILDBIRTH

Each year about 400 young mothers are admitted to mental hospitals in England and Wales with a diagnosis of "puerperal psychosis."[1] Even this number, however, probably represents only a part of the total mental illness associated with childbearing, for milder cases are not admitted to hospital, acute cases of short duration are often treated in observation wards, and finally many psychiatrists in mental hospitals do not return their cases in the puerperal category but use the appropriate descriptive diagnosis. There is much justification for this last practice, as no single clinical picture is associated with childbearing. E. W. Anderson,[2] C. Tetlow,[3] and M. A. White and colleagues[4] have all shown that a control group of non-childbearing women admitted to mental hospitals and matched for age will have a similar distribution of diagnoses to a childbearing group. Nevertheless, the occurrence of mental reactions at this particular time is not purely due to chance, for it is generally agreed that only about one in five mental illnesses associated with childbearing occurs during pregnancy, while four in five occur in the puerperium. Pregnancy, on the other hand, lasts approximately six times longer than the puerperium. The childbearing period clearly has some peculiar properties, but what these are no one seems to know. Psychological reactions are often seen in people who adopt children[5] and also in fathers[6] at the time of their wives' pregnancies, to give two types of situation in which any immediate somatic link with the new arrival is absent. White and colleagues[4] list a number of situations from which psychological difficulties may arise in childbearing patients—an unstable marriage, immaturity, an unwanted baby, and so on, and these authors claim that the importance of somatic disease is on the decline. Physical illness of the mother was only the seventh most important precipitating factor in their series, but against this their cases were not entirely "puerperal" in onset. Other studies report 25–50% of somatic complications, and H. Vislie[7] shows, as might be expected, that these are most commonly associated with confusional symptoms. A sidelight on this aspect which requires further elucidation is the finding by W. S. Wiedorn[8] in a retrospective study that 83.3% of schizophrenic mothers had a history of eclampsia as against only 34.1% of controls of like parity.

Childbearing creates special social conditions, and these probably account for the fact that significantly more childbearing mental patients leave hospital against psychiatric advice than non-childbearing controls. Unfortunately, too, the premature leavers are found to fare less well than those who complete treatment.

Recurrence of a reaction associated with childbirth occurs in only about one in seven mothers. It appears to be a rare indication for termination of pregnancy, and M. Ekblad[9] reports from Sweden that, of 479 abortions performed for psychiatric indications, only one was for a history of "puerperal psychosis." The advice given to a mother on whether to have more children is based on her life situation, her stability, and her attitude to the child. Detailed knowledge of the psychological changes and stresses of childbearing is scanty, and prophylaxis and prognosis suffer accordingly.

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THE HAEMOPHILIC DEFECT

The concept of haemophilia as a deficiency disease has developed gradually from accumulated evidence. First it was observed that a specific fraction of normal plasma —antihaemophilic globulin or A.H.G.—would shorten the clotting time of haemophilic blood.[1 2] Later it was found that A.H.G. was necessary for normal formation of blood thromboplastin.[3] This finding offered a possible physiological explanation for the haemophilic defect. The concept was elaborated by means of quantitative methods for the assay of A.H.G., and it was found that the tendency to bleeding is well correlated with the level of A.H.G. in the blood.[4] Moreover, the success or failure of surgical treatment in haemophilic patients apparently depends on ability to raise the patient's blood level of A.H.G.[5] All this evidence supports the hypothesis that the haemophilic defect is due to absence or deficiency of A.H.G. in the blood. Yet haemophilic patients are notoriously resistant to treatment. A severely affected patient may require A.H.G. equivalent to 5,000 ml. of fresh plasma to produce an effective haemostatic concentration.[5] The A.H.G. disappears rapidly from the blood,[6] response to repeated doses becomes progressively less,[5] and a small proportion of patients develop easily demonstrable circulating anticoagulants.

These features are difficult to account for on the hypothesis that haemophilia is a deficiency disease, and Tocantins and his co-workers have long held the view that the haemophilic defect is due to an anticoagulant. F. Nour-Eldin and J. F. Wilkinson[7] have offered new evidence for the presence of an anticoagulant in the blood of both haemophilic and Christmas-disease patients. They suggest that, though these diseases are fundamentally deficiency diseases, the severity of expression in a particular patient depends on the presence or absence of an anticoagulant called the Bridge anticoagulant.

Although the haemophilic defect is poorly corrected *in vivo*, it is apparently easily corrected *in vitro*. One part of normal blood added to nine parts of haemophilic blood will restore the clotting time to normal and greatly improve the results of the prothrombin-consumption test. No anticoagulant is revealed by these simple tests, and the search for them depends on indirect methods. Nour-Eldin and Wilkinson have based their method on the thromboplastin-generation test. Methods such as this are affected by many variables; for example the concentration of calcium will influence the results, as will also the level of antihaemophilic globulin or Christmas factor. The clinical significance of a particular pattern of findings will depend on the correlation between the clinical state of the patient and the results of laboratory tests. Observations which record the relative effects of A.H.G. level and supposed inhibitor, and an attempt to assess the inhibitor quantitatively in the absence of contamination with A.H.G., will be awaited with interest in order to establish the correlation without doubt. For the time being it would be wise to base practical assessment of severity and response to treatment in haemophilic patients on the results of quantitative methods for the measurement of antihaemophilic globulin. These methods have been proved in practice to give reasonably useful information.

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THE PLIGHT OF THE REGISTRARS

For three years the Joint Committee under the guidance of Sir Russell Brain has persistently and patiently discussed the plight of the senior registrars with the Ministry of Health, and now for the first time it has been made plain by the Minister that the principal, if not the only, obstacle in the way has been finance. The correspondence between Sir Russell Brain and the Minister published in this week's *Supplement* provides yet another example of the immovability of the bureaucratic mind. A number of senior registrars have already exceeded their time of training and are passing into middle age frustrated in their ambitions and penalized economically because the Treasury will not allow any more money to be spent on expanding the consultant establishment, although on medical grounds it appears that such expansion is much needed. The Minister of Health told the House of Commons on Monday that time-expired senior registrars should be given the opportunity of remaining in the hospital service pending at least the report of the working party to be set up to study the medical staffing of the N.H.S. hospitals. The Minister stated that he is asking hospital boards to submit proposals for designating a limited number of senior registrar posts which will carry a higher rate of pay and security of tenure for a limited number of those registrars who have completed the normal period of appointment. They will be responsible for the work which is normally expected of a fourth-year senior registrar, and the Minister is emphasizing to boards that the posts will not be a substitute for additional consultant posts. Both the Joint Committee and those representing registrars are opposed to this suggestion. They see in this new type of post the introduction of the assistant consultant grade, the institution of which is resolutely opposed by the Joint Committee. Neither the Joint Committee nor the registrars will be deceived by any implied promise that this would be merely a temporary expedient. The Ministry is adept at making the temporary permanent. It is difficult to understand why the Minister—or should we say his expert advisers?—will not accept Sir Russell's proposal that this decision should be postponed at least until the working party has reported. In his letter of April 18, the Minister refers without ambiguity to "the new posts." The grade of assistant consultant is thus being introduced because the country having willed the end refuses to provide the means, refuses, in other words, to give the people of this country enough responsible consultants, and to pay them properly for the responsible work they are called upon to do.

IMPACT OF NEW METHODS OF TREATMENT IN A PROVINCIAL MENTAL HOSPITAL

BY

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Increasingly and against severe administrative difficulties it is emerging in the mental hospital that work, as an activity in itself, and as a convenient and important medium for the establishment, maintenance, and deepening of interpersonal and group relationships, is of great value in the treatment of the major mental disorders and the resocialization of the chronic patients in mental hospitals. The denial to chronic patients of the right to relate themselves, through work, to their fellow men is one of the glaring anomalies of present-day mental hospital organization and management. This matter has become of much greater significance since the introduction of the drugs known as tranquillizers, whose place in treatment of mental disorders is already assured and by whose use, either alone or together with well-established methods of treatment such as E.C.T., the disruptive effect of psychotic tension can be virtually eliminated. One would expect a significant alteration in the pattern of mental hospital statistics with the application of the total therapeutic resources now available, and particularly since the introduction of the tranquillizing agents and the demonstration of the importance of a programme of rehabilitation.

The purpose of this paper is to describe the application of a programme of work and occupational therapy combined with increased nursing interest, together with the energetic use of the tranquillizing drugs and E.C.T. in a provincial mental hospital over a period of 18 months from January 1, 1956, to June 30, 1957, and to review the results obtained.

The hospital has 710 beds (368 male, 342 female), and is situated 2½ miles from the county town of 40,000 people. In the county there are four or five small towns, and the total population served by the hospital numbers more than 300,000. The medical staff consists of a superintendent (consultant), two assistant psychiatrists (senior hospital medical officers), and two junior hospital medical officers. During the period under review there was one occupational therapist, and since November, 1956, there has been an almoner. The nursing staff is shown in Table I. These figures compare unfavourably with those of other mental hospitals in Scotland and with the national average.

Position on January 1, 1956

The hospital is divided into a male and a female side. In January, 1956, the male side consisted of the admission ward of 30 patients and six wards for long-stay patients, each ward having between 30 and 40 patients. There was only one unlocked ward; 32 male patients were non-ambulant and 50 were able to work out of the wards, mostly in the hospital gardens under supervision. The remainder of the male hospital population were not engaged in any activity besides domestic duties in each ward, the majority spending most of the day sitting on benches in each of the ward's day rooms. The female side in January, 1956, consisted of one admission ward of about 30 patients and seven wards for long-stay patients, each ward having between 30 and 40 patients. Only one ward was unlocked and there were 72 female non-ambulant patients. There was no regular occupation for the majority of the female patients although the small occupational therapy department took 10 to 15 women a day, and a number of others worked in the kitchen, in the laundry, and in general sewing work for the hospital.

TABLE I

	January, 1956		January, 1957	
	Male	Female	Male	Female
Qualified nurses	31	16	41	22
Nursing assistants	8	20	7	16
Student nurses	4	6	6	11
Total	43	42	54	49
Staff/patients ratio	1/6·5	1/7·6	1/4·7	1/6·3

Table II shows the admissions, discharges, deaths, total hospital population, drug costs, and costs per patient-day for the years 1951–7. It will be seen that the admission and discharge rate before 1956 is comparatively low and the total hospital population is fairly stabilized. The drug bill shows a tendency to increase, as does also the cost per patient-day. Before 1956 many cases were refused because of lack of accommodation. From January 1, 1956, no patients were refused. Most cases were admitted by direct referral from general practitioners in the area, following interview at psychiatric clinics or domiciliary consultations, or by direct transfer from general hospitals. A vigorous attempt was made at all times to treat patients outside hospital if possible.

Introduction of a Programme of Rehabilitation

In January, 1956, an attempt was made to improve the conditions mentioned above. On the male side long-stay patients were classified according to behaviour and activity into seven groups. Three groups of 15 men each were able to work in the hospitals and gardens as before. One nurse was allotted to the special care and attention of each of the remaining groups of 10 patients whose behaviour ranged from severely deteriorated to "markedly less disturbed." For the deteriorated group there was initially habit-training

TABLE II

Year	Admissions			Discharges			Deaths			Hospital Population*			Costs March 31 Yearly		
													Per Patient/Day		Drugs
	C	V	Total	C	V	Total	C	V	Total	M	F	Total	Hospital	Regional Average	
													s. d.	s. d.	£
1951	49	8	57	20	5	25	57	0	57	305	278	583	8 8	12 6	489
1952	84	76	160	38	54	92	52	2	54	294	287	581	9 11	13 0	503
1953	97	94	191	47	80	127	49	7	56	299	299	598	11 2	13 9	1,005
1954	79	75	154	37	64	101	51	7	58	283	307	590	12 4	14 2	1,035
1955	76	108	184	44	89	133	35	5	40	271	315	586	12 5	14 10	1,102
1956	111	332	443	173	229	402	61	7	68	282	308	590	15 5	16 0	2,004
1957/ to 30/6	57	176	233	54	163	217	17	5	22	254	308	562	16 2	17 7	4,487

C = Certified. V = Voluntary. * At June 30.

and later work varying from ashing hospital paths to grass-cutting, lawn-mowing, or gardening. For the other groups of less-disturbed patients the programme consisted of such work in the occupational centre as wood-cutting, locker construction, formica-covering of tables. There was also physical training and games, gardening in individual plots, and group discussions, using as a basis a schools educational broadcast on current affairs or an educational film. A specimen programme is shown in Table III.

TABLE III

Work Period	Monday	Tuesday	Wednesday		Thursday	Friday	Saturday
9.30–10.30 a.m.	P.T.	P.T.	P.T.		P.T.	P.T.	Garden work
10.45 a.m.–12 noon	Group discussion	Educational film	Current affairs (schools)		Occupational centre	Garden work	P.T. games
2.30–3.30 p.m.	Individual gardening	Bowling	P.T. games	Visiting hours	Schools broadcast	Film show	Visiting hours
3.45–5 p.m.	,,	Gardening	Individual gardening		Nature ramble	,,	

As the scheme progressed a successful attempt was made to employ larger and larger numbers of patients on outside farm work and indoor assembly work (Miller, 1957). Nursing participation in the actual physical work being undertaken by the patient was encouraged, so that each group formed a team in which the nurse played the part of leader, spending almost his entire working-time in the company of his patients. Five to eight active patients remained behind in each of the wards to assist in the general domestic duties. The patients were encouraged to work by payment of a small sum of money (5s. or 7s. 6d. weekly, according to quality and standard of the work). Later an incentive was provided by their ability to earn a wage at outside farm work.

On the female side, because of the number of patients over middle age who were not physically active, shortage of suitable occupations, and shortage of nursing staff, the group nursing methods were not introduced to the same extent. The occupational therapy department, however, devoted itself to the treatment of women patients, taking 60 long-stay patients daily. A physical training class was started, performing simple routines such as marching, dancing, exercises with medicine balls, etc., to take 35 patients each morning; and a badminton class was begun. Some other patients worked on small individual plots in the hospital grounds, cultivating vegetables and flowers; and a group of 15 to 30 women were able to work outside the hospital, mainly at farm work.

Use of Electric Convulsion Therapy and Tranquillizers

Coincidently with the above programme and using the commonly accepted indication for the administration of E.C.T. (that of affective abnormality) and those of psychotic tension, overactivity, excitement, and aggressiveness for the administration of tranquillizers, these two treatments were given a trial, as follows:

Male patients: 16% of the long-stay patients had a trial of chlorpromazine alone; 7.6% had a trial of E.C.T.; 23.2% had a trial of E.C.T. together with a tranquillizer; and 1% had a trial of reserpine.

Female patients: 37.2% of the long-stay patients had a trial of chlorpromazine alone; 5.2% had a trial of E.C.T. alone; 16% had a trial of E.C.T. and a tranquillizer; and 8% had a trial of reserpine.

Accurate figures of the occurrence of jaundice are not available, but no more than 10 cases occurred during the period under review. There were no deaths attributable to the use of tranquillizers. Two deaths occurred in chronic patients within 24 hours of the administration of modified E.C.T. The causes of death were coronary thrombosis and fat embolism.

Improvement of Living and Social Conditions in Hospital

A general attempt was made to improve living conditions in the widest sense for the patient in hospital. The wards were decorated in turn, using light pastel colours. Harmonious colour schemes were obtained from the free advice of a colour consultant. The dietary of the patients was generally improved. Dining accommodation was improved by the introduction of stacking chairs and tables for use in each of the wards, thus removing the institutional atmosphere of dining *en masse* and releasing the dining-hall for use as an occupational centre. Patients were individually measured for new clothing and obtained a working suit of clothes and a suit to be worn in leisure hours. Latterly television sets were obtained for eight of the wards. A social club was formed for the patients and run by them. More dances were organized, and an increased number of outside societies and concert parties visited the hospital and willingly came to provide entertainment. An increased contact with the general community came through an increase in hospital visiting hours, from twice weekly to daily visiting, and by encouraging visits from outside clubs, social groups, guilds, etc., to come and see the hospital. Relatives were encouraged to take patients on week-end leave.

Position after 18 Months

The admission and discharge figures for 1956 and 1957 show a dramatic rise. At the same time there has been a fall in the total hospital population. A discharge rate of 90% was achieved in 1956, and for the first six months of 1957 the figure was 93%. The death rate has dropped. Despite the thrice-increased admission rate, the total hospital population has fallen from 600, at January 1, 1956, to 562, a fall of 7% and the number continues to fall. The drug bill has increased, but this is not serious when taken in conjunction with the greatly increased number of patients treated. The cost per patient-day has increased, but is still below the regional average and probably well below the national average. During this eighteen-month period 56 patients who had been in hospital for more than two years were successfully discharged to the community. Of these 56, 5 had been in hospital for more than 20 years (2 female and 3 male), 10 for more than 10 years (3 female and 7 male), and 15 for more than five years (10 female and 5 male).

Table IV shows the number of patients admitted during the period who were still in hospital on September 30, 1957. It will be noted that the majority of patients who have

TABLE IV

	Schizophrenics	Senile Dementia	Organic Dementia	Affective Disorders	Others
Male	12 (4)	3	6 (2)	4	7 (1)
Female ..	9 (1)	18	14 (1)	13 (1)	2

Transfers from other hospitals are bracketed.

remained are not schizophrenics but suffer from senile or organic dementia. Many suffer from a complication of physical illnesses as well, which helps to prevent their discharge. Twenty-one women were over the age of 70 and 14 over the age of 50. Three of the males were over the age of 70 and 12 over 50 years.

Improvements Within the Hospital.—The hospital has now only one locked ward for male patients and none on the female side. No more than 10 patients were non-ambulant in the hospital at the time of the survey, September 30, 1957. A large number of patients, both male and female, were able to go out of the hospital to work, with considerable financial benefit to the Department of Health.

The totals vary according to season but are in the region of 50 men and 15–30 women daily, at peak periods.

There is much less resistance to admission and there is a better feeling towards the hospital in the general community. The hospital has become a treatment centre for acute cases and at the same time a place where those patients whose illness does not respond initially to treatment can remain, able to maintain, through occupation and the use of drugs, meaningful relationships with other people in their environment whether it be patients, nurses, physicians, relatives, or friends, until their illness has resolved, or at least their behaviour has modified sufficiently to allow of their consideration for discharge.

Comments.—These results have been obtained by the intensive application of fairly new yet already well-tried methods. They have been achieved by a small medical and nursing staff, despite the vast increase in the out-patient and domiciliary services. The cost for the treatment of each patient has increased, but is still less than the regional average. There has been no capital expenditure in the construction of new premises. Accommodation for occupational centres and the occupational therapy department has been obtained by intelligent improvisation and by making use of the accommodation left vacant as a result of the increased discharge rate. The utility of the programme would seem to be unquestionable in terms of service to the community and improving the lot of long-stay patients in hospital.

Conclusion

It would appear from this short-term review that even without greatly increased medical or nursing staff, without greatly increased expenditure of money, without new buildings, and with only the present facilities and therapeutic resources available, the mental hospital can be run as an efficient unit, the problem of overcrowding can be solved, the accumulation of schizophrenics can be reduced to manageable proportions, and the chronic patient returned successfully to the community.

I thank Dr. H. J. B. Miller, physician-superintendent, Glengall Hospital, Ayr, for allowing me to publish this article.

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AUSTRALASIAN MEDICAL CONGRESS (B.M.A.)

TENTH SESSION IN TASMANIA

[FROM A SPECIAL CORRESPONDENT]

The tenth session of the Australasian Medical Congress (B.M.A.) was held in Hobart, the capital city of Tasmania, from March 1 to 7, 1958, under the presidency of Mr. J. B. G. MUIR, a Hobart surgeon. It was a major undertaking for the Tasmanian Branch of the B.M.A. to accept responsibility for the organization of such a gathering, but enthusiasm and much hard work, especially on the part of the honorary secretary of the Congress, Dr. FRANKLIN FAY, overcame all the difficulties and the Congress was a great success. Full co-operation was given by the various public authorities, especially by the University of Tasmania.

The Governor of Tasmania, Sir RONALD CROSS, opening the Congress, said that in all Australia there was no organization more highly regarded than the British Medical Association, and he extended to all visitors a warm welcome from the friendly Tasmanian community. The Congress had only once before been held in Tasmania, in 1934; and since the Commonwealth of Australia consisted of two islands, a northern island and a southern island, he felt that there must be some very good reason why the sessions of Congress were not held alternately in one island and the other. He was sure that many of the visitors should spend more time in Tasmania, such a paradise on earth it was. He found it hard to express the keen appreciation that laymen had of medical research, knowledge, experiment, and practice. Laymen had trust in and respect and affection for the men who worked early and late at all sorts of unseasonable hours to bring succour to those in need.

"The Health of the People"

Mr. J. B. G. MUIR then delivered his presidential address on "The Health of the People," a phrase which he traced back to Pericles, who in his oration to the Athenian dead had defined health as that state of moral, mental, and physical well-being which enables a man to face any crisis in life with the utmost facility and grace. Many centuries later Disraeli had spoken on the health of the people, defining it as "the real foundation on which all their 'happiness' and all their power as a State depend." In other words, besides including an important medical factor, in so far as the physical health of the individual was concerned, the maintenance of the health of the people had progressively become a vital political and economic force throughout history. The medical profession was directly or indirectly connected with all aspects of the health of the populace in an advisory capacity, but directly and in a practical way with the health of the individual in every aspect of disease.

Modern medicine was costly, continued Mr. Muir, not so much because of individual fees as because of the multitude of estimations and tests required for the proper conduct of a complicated illness. However, no member of the community was debarred because of expense from any measure which would help to cure him. Public hospitals covered those in the low income group, and health insurance was available to all. On the question of whether the cost of medical care was excessive, too much of a financial strain on the wage-earner, opinions would naturally be based on the success or otherwise of the treatment given. However, there was a general feeling that State assistance was indicated in some measure.

A number of people would advocate a completely free national health scheme such as there was in Britain, but the great and increasing cost of such a service should be remembered. Moreover, the general practitioners working under the British scheme were far from happy and contented in their work, and were completely under the control of the bureaucratic machine. Experience had shown that when services were free they were not appreciated, and exploitation of the doctor's time with frivolous consultations was a frequent occurrence. Time-consuming filling-in of forms and certificates was inseparable from any medical scheme, but appeared to be much worse on a full-time basis.

Insurance Scheme Advocated

To prevent exploitation, each individual should bear at least part of the cost of his illness, small enough not to cripple him financially, but enough to make him appreciate his responsibilities, to prevent abuse of the system, and to contribute towards the total cost. Medical and hospital insurance could cover the need if it was made universal and compulsory, and if it accepted for treatment all human ailments, particularly pre-existing disease. Norway had adopted such a compulsory health insurance policy after a slow and carefully planned evolution. It had, in fact, managed to combine "compulsory health insurance with maximum freedom for the doctor to pursue his own career in a system which brings out a maximum sense of responsibility in both the physician and patient."

Obviously some such scheme, covering all sections of the community and which would also permit free practice by the profession, was the best scheme for promoting a high standard of health in the people, because medical advice would be sought early in illness without fear of expense. It had always been the aim of the British Medical Association to uphold the complete freedom of the doctor in his practice. The most important assets of a doctor were the

good will and esteem of the public, and these could be earned only by service—in other words, by hard work and sympathy.

It was of questionable value to a patient if his life was saved or prolonged by skilful medicine or surgery, if afterwards he had to live under a financial strain to pay off his medical debts. Some comprehensive form of health insurance was the basic solution to this, but co-operation by the medical profession was essential. If a fee-for-service system arose so that corresponding health benefits became purely nominal, people would become disillusioned with a scheme which did not give them real financial relief when they were in medical trouble. The profession had a responsibility for guiding patients through medical channels appropriate to their financial means as well as to their illness. Despite its evolution into an accurate and itemized science, medicine would still remain a healing art, provided, as Newman had put it, the one essential was maintained—the old professional spirit which had underlain the practice of medicine in England and the Commonwealth, about which one never spoke and which was never taught: the professional spirit of putting the interest of the patient above the claims of gain, of fame, of research, and of the State.

Mr. Menzies on Science and Civilization

The third Henry Simpson Newland Oration was delivered by the Prime Minister of Australia, the Right Honourable R. G. MENZIES. In it Mr. Menzies considered the place of modern science, including military science, in civilization. He stressed the importance of not allowing spectacular modern scientific developments to assume a disproportionate position in present-day thinking or to affect the appreciation of essential values. He agreed that it was important to produce more and better scientists in answer to such things as the sputniks. But the important issue was what the scientists were to be produced for. Scientific activity for defence was solely a means of preserving democratic freedom and civilized individual rights.

Scientists and scientific research were required to provide for the material future of the people; but the housing, feeding, clothing, and curing of mankind, though vital and imperative, were not an end in themselves. They were the means to a great end. As an instrument, science could achieve either good or ill. It would depend on the minds and spirits of those who used the instrument. If science was truly to serve the cause of civilization, it would be because the people who used the advances of science had grown to use them in a civilized way. Mr. Menzies quoted his own words from another recent speech: "Let us have more scientists and more humanists. Let the scientists be touched and informed by the humanities. Let the humanists be touched and informed by science, so that they may not be lost in abstractions derived from outdated knowledge of circumstances." Not all the most brilliant successes in laboratories and factories and fields would make a nation great in history's eye if it had failed to enthrone the human spirit, and to set about it knowledge and justice and patience and understanding.

Scientific and Academic Programme

The scientific programme occupied three and a half days, one afternoon being taken up with a garden party given by Sir Ronald Cross and Lady Cross at Government House. The first day of the scientific meetings was given over to three plenary sessions. Thyroid disease was discussed by Dr. W. E. KING, Dr. F. W. A. CLEMENTS, Dr. W. P. HOLMAN, and Dr. G. R. A. SYME from the point of view of its medical aspects, public health, and its treatment by radiation and surgery; Dr. W. B. MACDONALD and Professor MAURICE EWING discussed the use of fluids and electrolytes in health and disease; and in a symposium on heart failure Dr. B. SINCLAIR-SMITH discussed the physiological mechanisms in heart failure, Dr. JOHN HALLIDAY its management, and Dr. IAN MONK the role of the surgeon in the presence of heart failure. The remaining two and a half days were given over to meetings of the various sections, which on many occasions joined together in combined meetings.

The Council of the University of Tasmania conferred honorary degrees on three distinguished visitors: Mr. Menzies; Sir Charles Bickerton Blackburn, of New South Wales; and Sir Alexander Paterson Murphy, of Brisbane. And the president of the Federal Council of the British Medical Association in Australia, Dr. H. C. COLVILLE, on behalf of the Federal Council presented the University with a gavel made of Tasmanian blackwood, to commemorate the Congress. Dr. Colville also presented the Henry Simpson Newland prize in surgery to Dr. NEVILLE DAVIS, of Queensland.

NEOPLASIA: A CONFERENCE IN GLASGOW

A conference on "Neoplasia" was held in Glasgow from March 26 to 28. It was arranged by the postgraduate medical education committee of the University and the Royal Faculty.

Aetiological Factors

Dr. P. R. PEACOCK (Royal Beatson Hospital), the opening speaker, said that, although theoretically cancer could start from a single cell, the earliest case he personally had seen was multicentric. In addition to the definite neoplastic foci, there were areas of retained secretion in this case, and they must consider the possibility that the retained secretion was carcinogenic, especially in view of recent suggestions that cholesterol is a carcinogen. Perhaps cholesterol could be transformed into methyl cholanthrene. Apart from a few industrial cases the cause of carcinoma was unknown, and even where the carcinogen was recognized the final process still remained to be elucidated. Possibly contaminants of so-called carcinogens would prove the active agents. He regarded cancer as an alternative mode of existence for a cell threatened by death; it might be a consequence of imbalance of the cell constituents.

Professor J. N. DAVIDSON then reviewed what is known of cell substances, notably those of the nucleus. The most important of these was desoxyribonucleic acid (D.N.A.). The cellular content of D.N.A. was remarkably constant in different organs except for the liver, where it was increased; also many tumour cells had more D.N.A. than normal cells. D.N.A. might actually alter the characteristics of cultures and even of organisms—for example, D.N.A. from a mutant added to a sensitive culture would produce mutant cells in the culture. Dr. R. J. C. HARRIS (London) spoke on the virus theory of cancer, and of his attempts to produce immunological tolerance to allow viruses causing tumours in one animal to be transferred to another animal.

Dr. B. D. PULLINGER said that recently many mammary tumours had been found to be associated with cholesterol deposits, and cholesterol was also known to have caused carcinoma in the bladders of mice. Hormones had been studied intensively, first by Beatson in Glasgow in 1896; and in 1932 Lacassagne had produced tumours in mice with oestrogen. Bittner had shown in mice that milk might transmit a factor giving rise to mammary tumours, while recently carcinoma had been produced by local injections of oestrogen. Some doubt had been cast upon the importance of these hormones, however, because in spayed mice substituted hormones produced no increase in tumours, and it was suggested that a genetic predisposition might be more important than the added hormones.

Dr. A. T. DOIG discussed industrial cancer and the industries in which it occurred, emphasizing that the latent periods might be prolonged. The possible factors involved were tar, pitch, shale oil, asbestos, *x* rays, ultra-violet rays, arsenic, and chromates; and more recently radium and other radioactive materials had become important. In some industries substitution of non-carcinogenic materials might be practicable, in others the process could be properly screened. He made a strong plea for the notification of all

possible cases of industrial cancer, so that the conditions of work might be examined.

Leukaemia and the Reticuloses

On the second day Dr. R. I. SHAW DUNN discussed the pathology and classification of tumours of lymphoid tissue. In animals this tissue was associated with the haemopoietic system and the alimentary tract. The peripheral nodes were more recent phylogenetically, and most diseases of lymphoid tissue affected them.

Dr. ALEXANDER BROWN dealt with the clinical picture of "reticulosis." Leukaemia was merely a symptom, he said, and might occur in several different diseases. There had been a gross increase in leukaemia after atomic bombing and in radiologists; but over the same period its incidence in the general population had also increased. The prognosis in these diseases of the reticulo-endothelial system was poor, the average survival being two and half years, although a patient with Hodgkin's disease might last several years and a patient with chronic leukaemia for up to twenty years. At present treatment was non-specific, being aimed at the abnormal pattern. *X* rays might be used locally, whereas chemotherapy was usually reserved for radio-resistance and for after generalization.

Dr. A. R. CURRIE reviewed a series of eight cases, characterized by anaemia, leukaemia, and thrombocytopenia, in which tumour cells were sometimes isolated. In general the liver cells and lymphoid nodes were not involved. The series appeared to include cases linking Hodgkin's disease, leukaemia, and tumour.

Regional Cancers

Mr. A. P. M. FORREST, who discussed breast cancer, said that, although many attempts had been made to use histological and hormonal characteristics for prognosis, none had been wholly successful. Mr. W. B. STIRLING described the greatly improved results of treatment of prostatic cancer over the last 20 years. Only 5% of cases were suitable for radical prostatectomy; the rest were treated by stilboestrol. After stilboestrol the average prognosis improved from the untreated case's 15 months (with 9% 5-year survivals) to 45 months (with 27% 5-year survivals). Adrenalectomy had not proved very helpful, and hypophysectomy gave poor results.

On the last day the opening speaker was Professor J. W. ORR (Birmingham), who discussed liver cancer. In Africa primary liver cancer was very common, but racial factors seemed to have little to do with it, since negroes in America did not show this tendency. The explanation might be a dietetic deficiency or some toxic factor. Probably the cancer developed on top of a process of regeneration.

Professor C. F. W. ILLINGWORTH drew attention to the poor results of the treatment of carcinoma of the stomach, a disease which now caused the death of 300 people a week in the United Kingdom. The 5-year survival rate of diagnosed cases was only 2.7%, and of cases after resection 12%. The aetiology was unknown. It was not possible to produce tumours in animals by feeding carcinogens, and probably no more than 5% of gastric ulcer cases became malignant. In treatment radical total gastrectomy was unsatisfactory; partial gastrectomy was probably best. Professor Illingworth then described his own work on exfoliative cytology, and said it had not added many to the cases diagnosed by other means. He suggested that the routine test for occult blood in the faeces might be a useful screening test for gastric cancer.

Dr. E. M. MCGIRR discussed cancer of the thyroid gland, which, he said, accounted for only 0.4% of deaths from malignant disease. It affected females more than males at all ages. Surgery was not very helpful and radioactive iodine was suitable for only 10% of cases. Mr. R. S. BARCLAY drew attention to haemoptysis as an early sign in lung cancer, and showed examples of lung abscess, pleural effusion, unresolved pneumonia, and collapse due to neoplasm. Diagnosis should include bronchoscopy, bronchospirometry, and in some cases angiocardiography. Treatment should be conservative, only enough lung being removed to get rid of the tumour. Even with the best treatment, results were poor.

THE PULMONARY CIRCULATION

SYMPOSIUM IN CHICAGO

[FROM A SPECIAL CORRESPONDENT]

The Chicago Heart Association was responsible for a successful international symposium on the pulmonary circulation, held in Chicago from March 20 to 22. Papers were presented and discussed by 35 invited participants from the United States, Mexico, Canada, Britain, and Sweden, and the meetings were attended by over 500 doctors and research workers from all over North America.

The first session, under the chairmanship of Dr. JULIUS H. COMROE, jun. (San Francisco), was devoted to physiology. After Dr. ALAN BURTON (London, Canada) had discussed the pressure–flow relationships in the pulmonary circulation, and Dr. ARTHUR DUBOIS (Philadelphia) the use of the whole-body plethysmograph for determining the instantaneous pulmonary capillary blood flow, Dr. GEOFFREY DAWES (Oxford) read a paper on the reflexes originating in the pulmonary circulation. In certain species, he reported, a rise in pulmonary arterial or venous pressure led to a slight fall of systemic blood pressure; cutting the vagus abolished the response. The sites of the sensory receptors responsible for this reflex were still uncertain, but it seemed clear that there were both pressure and volume receptors in the left atrium. He also drew attention to a recent report that the pulmonary vascular resistance could be modified by changes in the oxygen content of blood perfusing the carotid body.

Dr. HARRY FRITTS and Dr. ANDRE COURNAND (New York) described their recent work on the effects of unilateral hypoxia on the pulmonary circulation. Ventilation of one lung with 4% oxygen was followed by a decreased blood flow through this lung—for example, a fall from 4 to 2½ litres per minute. To illustrate the complexity of the problem Dr. Cournand reported an experiment in which unilateral hypoxia led to a rise in pulmonary arterial pressure without any change in the relative blood flows to the two lungs.

Structural Changes

The second session was on pathology, with Dr. JESSE E. EDWARDS (Minnesota) in the chair. Dr. AVERILL A. LIEBOW (Yale) spoke on the relation of the bronchial to the pulmonary vascular tree, illustrating his paper with beautiful slides showing casts of the bronchial and pulmonary arteries in different colours. He presented evidence that, in the presence of extensive broncho-pulmonary arterial anastomoses, the pressure of the blood entering the pulmonary circulation might sometimes be so great as to cause a back-flow of arterial blood towards the pulmonary arterial trunk. But even under these circumstances there was no pulmonary hypertension. Dr. DONALD HEATH (Birmingham) described the structural alterations of the pulmonary vessels in response to pulmonary hypertension. He claimed that it was possible to distinguish cases in which pulmonary hypertension had been present from birth from those in which it had developed later in life by histological examination of the large elastic pulmonary arteries. If hypertension had existed from birth, the elastic laminae were regular, compact, and dense as in the aorta. If hypertension had developed later—for example, as in mitral stenosis—the elastic fibrils were less regular and of an open texture.

Dr. DONALD J. FERGUSON (Minneapolis) described the production of pulmonary hypertension in dogs by anastomosing the brachial artery to the pulmonary artery. At first there was a large shunt from the brachial to the pulmonary

artery. With the passage of time, the pulmonary arterial pressure rose and the shunt declined. Necropsy showed a greatly increased wall–lumen ratio (regarded as indicative of medial hypertrophy) and, in dogs which had survived for a long period, intimal thickening.

Dr. DAVID S. SHORT (London), however, questioned the validity of the term hypertrophy when used merely to describe arteries with an increased wall–lumen ratio. He pointed out that a similar appearance was produced by arterial contraction. In a subsequent paper on the application of arteriography to the pathological study of pulmonary hypertension, Dr. Short stated that the true extent of pulmonary arterial disease could be determined most accurately by the technique of post-mortem arteriography. This showed no significant reduction in the pulmonary arterial bed in controls, but a striking reduction in the arterial bed in every case of established pulmonary hypertension which had been investigated. The narrowing of the arterial lumen was due partly to obstruction within the lumen, either by organized thrombus or by intimal proliferation, and partly to a diffuse organic narrowing and indistensibility which he termed arterial contracture. This arterial contracture gave the appearance of hypertrophy.

Clinical Studies

In a session on the pulmonary circulation in primary lung disease, under the chairmanship of Dr. LARS WERKÖ (Gothenburg, Sweden), Dr. IRENÉ FERRER (New York) spoke on decompensated pulmonary heart disease. Dr. Ferrer stated that the treatment of failure in cor pulmonale was usually followed by a fall in cardiac output, while in right heart failure due to heart disease there was a rise of cardiac output with treatment. Dr. Ferrer suggested that the normal or high cardiac output in cor pulmonale was due to the fact that the myocardium was relatively intact until the terminal stages of the disease.

Dr. NOBEL FOWLER (Cincinnati) reviewed the effect of drugs on the pulmonary circulation, and concluded that, while certain drugs undoubtedly lowered the pulmonary arterial pressure, the evidence of an effect on the pulmonary vascular resistance was inconclusive. Even if the resistance was lowered, it might be an indirect effect. In discussion, Dr. S. GILBERT BLOUNT, jun. (Denver), produced evidence that, in young patients with ventricular septal defect and a pulmonary arterial pressure which was high but not as great as that in the aorta, the administration of tolazoline hydrochloride led to a striking fall in pulmonary arterial pressure with an increase in the left to right shunt. In a subsequent paper, Dr. PAUL WOOD (London) described how the injection of acetylcholine into the pulmonary artery in cases of mitral stenosis was followed by a sharp fall in pulmonary arterial pressure, a rise in pulmonary capillary venous pressure, and an apparent halving of the pulmonary vascular resistance.

Congenital Heart Disease

Dr. HOWARD BURCHELL (Rochester) took charge of the session dealing with the pulmonary circulation in congenital heart disease. Dr. DAWES reviewed the evidence on the time of closure of the ductus arteriosus. In the larger farm animals the ductus remained open for some time after birth. Continuous murmurs could be recorded by phonocardiography, and a passage of dye from the aorta into the pulmonary artery could be demonstrated by cine-angiography. Dr. Dawes quoted reports of the detection of arterialized blood in the pulmonary artery of babies soon after birth. He also mentioned an unpublished communication of the finding of a ductus murmur in about one-third of newborn infants.

Dr. LEWIS DEXTER (Boston) dealt with pulmonary hypertension in atrial septal defect. He emphasized the rarity of pulmonary hypertension in those under the age of 20 with this condition, and the importance of thrombosis in the pathogenesis of the hypertension. In discussion, Dr. JESSE EDWARDS expressed the view that the thrombosis was mainly a terminal event. With regard to the regression of the pulmonary vascular changes after cure of intracardiac defects, Dr. HOWARD BURCHELL reported that, in the presence of pulmonary hypertension, closure of an atrial septal defect was followed by a fall of pressure, and sometimes of resistance, though the latter never fell to anything approaching a normal figure.

Pulmonary Oedema

The final session was given over to a consideration of the pulmonary circulation in acquired heart disease under the chairmanship of Dr. PAUL WOOD (London).

Dr. STANLEY SARNOFF (Bethesda) described some interesting experiments bearing on the development of pulmonary oedema. If the pulmonary veins were not distended, a small increase in blood content led to a negligible rise in pulmonary venous pressure, but if the veins were filled almost to the limit of their capacity a small additional quantity of blood led to a considerable rise of pressure. Stimulation of the vasomotor centre caused a great increase of aortic pressure due to widespread peripheral vasoconstriction. Blood was transferred from the systemic to the pulmonary circulation, leading to a sharp rise in left atrial and pulmonary venous pressures. Ganglionic blockade sufficient to give a small fall in aortic pressure led to a great fall in left atrial pressure. This was due to the fact that a slight release of systemic vasoconstriction permitted the transfer of a small quantity of blood from the pulmonary to the systemic circulation, so relieving the critically distended pulmonary veins. On the basis of such experiments Dr. Sarnoff felt that ganglion-blocking drugs were specific therapy for the pulmonary oedema of hypertension.

Dr. K. W. DONALD (Birmingham) spoke on pulmonary vascular resistance in mitral stenosis and insufficiency. He pointed out that a high pulmonary vascular resistance tended to be associated with a reduced lung compliance. This led to maldistribution of air and a reduced oxygen saturation of arterial blood.

Dr. Wood proposed a classification of pulmonary hypertension as follows :

Passive—elevated pulmonary venous pressure.
Hyperkinetic—increased pulmonary blood flow.
Obstructive—pulmonary embolism or thrombosis.
Obliterative—reduction of pulmonary vascular capacity.
Vasoconstrictive—functional reaction.
Polygenic—of multiple origin.

He then proceeded to consider particularly the vasoconstrictive factor in pulmonary hypertension. He described a technique for the injection of a single dose of acetylcholine into the pulmonary artery. The dose was so small that its effect was apparently limited to the pulmonary circulation. The systemic arterial pressure did not fall. In cases of pulmonary hypertension associated with mitral stenosis or chronic lung disease the injection of acetylcholine was immediately followed by a striking fall in pulmonary arterial pressure. A similar effect was observed in primary pulmonary hypertension. In pulmonary hypertension associated with congenital cardiovascular disease, on the other hand, there was no fall in pressure. These results seemed to indicate that in the group of cases which showed a fall in pressure there was an important vasoconstrictive element contributing to the hypertension, though not necessarily causing it.

Dr. DEXTER reported that, following relief of mitral stenosis, the pulmonary arterial pressure and resistance fell rapidly over the first two weeks and the figures were often almost normal at the end of a year. Dr. DONALD agreed, but stated that even after the best results the pulmonary vascular resistance rose abnormally on exercise.

Much of the value of this well-organized conference lay in the opportunity of informal discussion, and this was catalysed by the wonderful hospitality of our American hosts. It is planned to publish the proceedings of the conference.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Resettling the Disabled

SIR,—In the past year I have spent some months in an orthopaedic ward and have seen a good deal of accidental disabilities from the patient's side. You (*Journal*, April 5, p. 818)—and Charles Lamb—are of course right about many disabled people finding it fatally easy to don the "strong armour of sickness." They do not even need to "put on" this armour—willing hands reach out from all directions to fasten it for them. No blame is attached to them, in the early stages, for wearing it; that comes later when everyone sees it for the trap it is. The patient's family and friends, and those whose task it is to help with his resettlement, in the home circle or at work, are apt to overdo the tempering of the wind. Their help should be directed towards getting the man or woman a place in the community as close as possible to the one they used to occupy.

The man who breaks his leg in a motor-cycle accident or catches his fingers in a saw, so that he suddenly acquires a permanent disability, gets on well enough in hospital, where even pain is shared with others in similar or worse predicaments. Even the worries of compensation, damages, and the future seem remote in a hospital bed. It is on his discharge that the disabled man's troubles really start, when he is still unfit to see the arrows of outrageous fortune in proper perspective, let alone oppose and end them. At this stage he runs a serious risk of being overwhelmed by a serious disability. The sense of his own futility may be terribly strong. At every turn he is reminded that his home and business can run without him—in some ways just as well if not better.

He may now realize for the first time that he is going to be permanently disabled. In facing the facts and making the best of them he can be immeasurably helped by a sound prognosis and well-informed advice on what he can still do, to stop him brooding unduly on what he cannot do. If he can grasp the true extent of his disabilities he may see the fascination and excitement, rather than the horror, of shouldering his handicaps and exploring his latent abilities. If he is to enjoy adapting himself to changed circumstances he will need all the encouragement he can get from his family, employers, and colleagues. He also needs reasonable freedom from anxiety. In accident cases a good lawyer can often be far more helpful in this way than medical advisers. Without legal advice some of the lads involved in motor accidents worry themselves stiff over nothing.

Disabilities sometimes last far longer and cause much more suffering than they need because nobody has studied them in detail. The disabled person's medical and surgical advisers can do him a great service by thoroughly assessing his disability and making sure that all possible steps are taken to reduce it and its unpleasantness to a minimum. Those who return from hospital in pain, or develop pain as they get more active, may wrongly assume that nothing radical can be done about it. The strong-minded grin and bear it needlessly, while some weaker mortals acquire the analgesic habit or follow tradition by taking to drink. Their doctors may save them from either fate.—I am, etc.,

Tonbridge, Kent. E. CLAYTON-JONES.

A Radial Neuropathy

SIR,—A feeling of numbness of the index finger and thumb makes one think of a lesion of the median nerve, and when tingling is obtrusive a carpal tunnel is immediately suspect. Unfortunately one has sometimes to depend entirely on the patients' description of the distribution of the symptoms, and since they find this difficult their statements may be misleading. A median neuropathy has now become a fashionable diagnosis, so that the following two cases may be of interest.

The first, a man of 60 years, complained of severe tingling in his left thumb and index finger for a year, and this had been constant for three months. This was most severe during the night and would often waken him. On examination there was a profound loss of all sensory modes in the distribution of the radial nerve, that is to say, on the radial side of the dorsum of the hand and the first phalanges of thumb and index finger. The triceps jerk was a little reduced but there was no weakness. At first he claimed that the tingling was felt throughout the two fingers, but on subsequent interviews he stated that this was most severe at the base of the fingers on their dorsal aspect. He said that the tingling seemed to run down the fingers.

The second, a man of 23 years, had two bouts of numbness of the left thumb and index finger lasting several weeks. At first he claimed that the numbness was felt all over the fingers, but subsequently he said that the numbness was most marked at the base of the thumb on its dorsal aspect. He continued to assert, however, that he had a slightly numb sensation at the tips of the two fingers. On examination there was slight loss of pain sense over the radial nerve distribution. There was very slight weakness of the triceps and extensors of the wrist and fingers, while the triceps and supinator jerks were slightly reduced.

Both patients said that they had the habit of sitting with their left arms over the back of a chair.

If one had accepted the original statements of these patients and had not tested carefully sensation of the back of the hand, the diagnosis might have been overlooked. Marked sensory symptoms referable to the radial nerve, even with marked weakness, are very unusual. Perhaps they would be found more often if the possibility was kept in mind.—I am, etc.,

Glasgow. STEWART RENFREW.

C.S.F. in Neurological Diagnosis

SIR,—Drs. M. Locoge and J. M. Cumings are to be congratulated on recording in so concise a manner (*Journal*, March 15, p. 618) such a vast amount of data concerning the content of cerebrospinal fluid (C.S.F.) in a large variety of neurological conditions. While providing information valuable to both clinician and pathologist, their paper rightly stresses how difficult it may be to assess fully the significance of any one abnormal (or normal) C.S.F.

As no details of technical procedures are presented, it is permissible to inquire how the identity of cells was established and also to present the following observations. So far as I am aware the method in use in most laboratories of assessing the percentages of polymorphs and lymphocytes in C.S.F. is by counting stained leucocytes in the haemocytometer used for the total cell count. This is a rapid and useful method, but its inaccuracies must be appreciated. Thus the "lymphocyte" (mononuclear would be a better term) may be a lymphocyte, a macrophage, a plasma cell, an arachnoid cell, or a malignant cell; and the polymorph may be neutrophil, eosinophil, or basophil. For accurate cell identification, stained films of the centrifuged deposit must be examined. The choice of staining method rests with the examiner, but I have found the Giemsa–May Grunwald technique most satisfactory.

Two cases recently encountered perhaps testify to the value of the above technique. The first was a woman of 51 who, some weeks after a febrile chill, developed a rapidly progressive paraplegia with some sensory impairment in the lower limbs, loss of sensation over the region supplied by the right trigeminal nerve, paresis of the left facial nerve, optic neuritis, and nystagmus. There was some neck stiffness, and the C.S.F. contained 900 leucocytes per c.mm. A differential count in the counting chamber (C.S.F. stained with 1% toluidine blue) suggested that the proportion of polymorphs present was 25%. However, examination of a stained film of the centrifuged deposit showed that almost all of the polymorphs were eosinophil, that a few were basophil, and that only an occasional neutrophil polymorph was present. It is not suggested that this rather surprising finding rapidly established the diagnosis, but it did help to rule out the possibility of some subacute bacterial infection. The cell count gradually returned to normal over a period of four to six weeks and the patient made a slowly progressive and ultimately almost complete recovery, a diagnosis of acute disseminated encephalomyelitis being made. I am unaware of any previous report of a similar meningeal cell response in this type of case, but it may be that it not infrequently occurs in acute neurological illnesses of

so-called "allergic" aetiology when accompanied by a pleocytosis in the C.S.F. It might be mentioned in passing that there was no demonstrable increase in eosinophils in the peripheral blood or in the sternal marrow in this case.

The second patient was a man of 19 with the progressive onset of subacute meningitis over a period of three to four weeks. On examination, he was drowsy and had early papilloedema, pareses of sixth and seventh cranial nerves, and a right-sided hemiparesis. He had a moderate neck stiffness, and, over the first two weeks in hospital, daily lumbar puncture showed a white cell count varying from 50 to 150 per c.mm. No acid-fast bacilli could be found, but it was thought that he was probably suffering from tuberculous meningitis—that is, until malignant cells were identified in a stained film of the centrifuged deposit of the C.S.F. Necropsy ultimately revealed a glioblastoma multiforme which had involved the leptomeninges.

I hope that the brief descriptions of these two cases will be thought to support my contention that accurate cell identification should be a routine procedure in the examination of abnormal cerebrospinal fluid.—I am, etc.,

London, S.E.5. J. HUME ADAMS.

Mass Radiography

SIR,—Dr. Charles Stewart's letter (*Journal*, April 5, p. 827) on the use of mass radiography is timely. Many people closely connected with the work of mobile units found the recent Ministry of Health report (H.M.(57)94) somewhat evasive and unconstructive as regards the future use of units. The recent television series *Your Life in their Hands* hardly mentioned the preventive side of tuberculosis, and mass radiography not at all. In many areas of the country mobile and static units are detecting over one-third of all active cases.

The planning of a mobile unit's work is not easy. When a static unit is available at hospital or chest clinic certain "priority" groups can be examined regularly—e.g., cases without definite chest symptoms referred by general practitioners for an excluding x-ray, contacts, National Service call-ups, etc. In other areas the mobile units return regularly to bases to deal with these selected surveys. But a year's work has to be adapted to the needs of the various chest clinics and to several medical officers of health for many areas—all with legitimate requests, and all with annual reports to compile dealing with parochial activities (including mass radiography). Although factory surveys are being extended to longer intervals, a very high proportion of the year's work at present is unproductive and uneconomical.

The first seven years of mass radiography was largely pioneering; in the second seven years the net widened and surveys attracted wider publicity and embraced fresh fields. The next seven years could be the opportunity for a planned "military" operation, not locally, not even at regional level, but partly on a national basis. At the onset some scheme could be devised on the following lines, making full use of the present organizing secretaries, and dividing the country into a few sectors, but with cities and great towns the chief objective on the lines of Glasgow and Edinburgh. The geography of regional hospital boards would not be taken into account necessarily. The working year could be divided roughly as follows: (1) approximately two months' work in the chief *cities* of each sector, making use of all available units; (2) approximately two months' work in the chief *towns* of regional board areas, but sometimes using units from other regions; (3) six months' work as at present, working in local clinical areas in liaison with chest clinics and M.O.H.s; (4) one month for leave and refitting, etc. The lessons learnt in Glasgow and Edinburgh would be studied and applied. Mass radiography is an integral part of the chest clinic and has become a *clinical* unit (a fact lost sight of by a few individuals), and the director is usually a member of the chest unit with full hospital facilities and beds.

If such a scheme were put into operation, the next seven years (on the Dutch pattern) could be a triumphal march. It could be expected that certain areas would need a few more beds for tuberculosis for a few years, after the recent happy reductions. It would require a small central organization to control the efficient use of all units. The cost of advertising and propaganda is a serious problem, but local authorities interested in complete eradication of the disease would no doubt help more in this matter.

I must add that these remarks represent my personal views only and not necessarily those of my hospital board, which, however, has participated with enthusiasm in the Glasgow and Edinburgh campaigns.—I am, etc.,

Cheltenham, Glos. J. B. W. HAYWARD.

Hormone Therapy and Rheumatoid Arthritis

SIR,—The letter on this subject from Christchurch, New Zealand (*Journal*, April 5, p. 828), made refreshing reading. I entirely agree that the gloomy tone of your leading article of November 30, 1957 (p. 1290), is quite unwarranted. We have patients with severe rheumatoid arthritis who have had oral steroids for over six years continuously, whose disease has been very satisfactorily controlled, and who have returned to and remained at work for that period.

However, the question of cortisone dosage for long-term treatment is still a difficult problem. Your Christchurch correspondents quote 6–10 mg. prednisone (which equals 15–60 mg. cortisone) as the range of practical safe therapy. This is surely much too inaccurate, and side-effects will still occur within this limit. As they point out, individualization of dosage is the ideal, but at the moment our methods of estimating this are still crude. We have only rough aids to measure suppression of the arthritis and only clinical evidence of side-effects to indicate overdosage.

In our study at the West London Hospital (*Journal*, November 30, 1957, p. 1257), which your correspondents quote, we used corticotrophin to determine the relationship between the suppression of symptoms and the urinary steroid output. In the future this or some similar estimation may become an additional aid to find the correct dosage. We were able to show that severe side-effects only occur with a considerable increase of steroid metabolites in the urine. The study also revealed that only minimal adrenal stimulation is necessary to maintain suppression of the arthritis. Further studies of the metabolism and excretion of adrenal cortical hormones and their end products in health and disease should enable physicians to estimate the required dose in each individual in a more scientific manner.—I am, etc.,

London, S.W.1. OSWALD SAVAGE.

Steroid Therapy in Apoplexy

SIR,—You have given a deserving lead on the subject of the immediate treatment of apoplexy by your annotation (*Journal*, January 7, 1956, p. 35). The subject is of paramount interest to a larger population day by day all over the world. Cortisone therapy has great potentialities and deserves wider trial in this condition.

It is unfortunate that Drs. Hetzel *et al.*,[1] of Australia, have decided to discontinue their therapeutic trial of corticosteroids in apoplexy, after reading the paper by Dyken and White.[2] The latter authors have not obtained favourable results with cortisone and have concluded that "there was a trend indicating that cortisone may be a dangerous drug to use in cerebral vascular disease." I believe that such a conclusion will do a disservice by bringing into disrepute a valuable drug in the immediate therapy of coma in cerebral infarction. After reading the article by Russek *et al.*,[3] we tried the treatment in about a dozen cases of cerebral infarction. We agree with Dyken and White, in so far that cortisone does not favourably influence the course of ultimate paralysis and does not help in decreasing the degree of neurological residua. We did not encounter "dangerous" consequences of the drug during treatment. Our impression (uncontrolled) was that the treatment helps the patient by curtailing the time required for subsidence

of paralytic phenomena to minimum residual neurological damage. It also has a beneficial effect on the patient's outlook and thus helps early rehabilitation.

Apart from the above finding, a more important advantage of the treatment emerged from our trial. The treatment proved to be very useful in bringing the patient out of coma in four cases when the usual conservative and supportive measures had failed and death seemed to be imminent. Let me quote one of the cases in support.

A male aged 70 became unconscious during sleep and could not be roused in the morning. He was removed to Sassoon Hospital and investigation suggested cerebral thrombosis as the only probable diagnosis. At the end of 48 hours on conservative treatment and supportive measures, the clinical condition was fast deteriorating—coma was deepening and reflexes were getting more and more sluggish. The relatives, clearly seeing that a fatal outcome was unavoidable, wanted to take the patient home to die. They were dissuaded on the ground that a valuable form of therapy was still untried and that it should be given a trial before hope could be completely given up. Cortisone acetate, 100 mg. three times a day, was injected subcutaneously. After the third injection the patient showed signs of improvement, and after three days on the same treatment he was completely conscious. He was discharged a fortnight later after tailing off the cortisone, and is healthy to this day, about six months after his discharge.

Thus we find that cortisone is invaluable in the treatment of coma of cerebral infarction. If this finding is borne out by the experience of other workers, cortisone therapy will have a place of importance in the immediate treatment of apoplexy. We are shortly publishing our experience of this treatment in a separate paper.—I am, etc.,

Poona. P. L. DESHMUKH.

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Grease-gun Injury

SIR,—Mr. A. J. H. Rains is to be congratulated upon the results he obtained in his case of a grease-gun injury (*Journal*, March 15, p. 625). His article is a valuable one, for it indicates the correct treatment of a condition which is likely to puzzle any doctor who has not read about it.

Mr. Rains's patient was fortunate, inasmuch as he sought medical attention immediately after the accident and went to a practitioner who appreciated the nature of the injury and treated it appropriately by incising the wound and expressing as much grease as possible. My own experience suggests that the right diagnosis is not always arrived at so rapidly. Under the high pressures obtained in some machines, oil can be blown into the fingers if they are merely placed in front of the injection nozzle, and without actual contact with it having taken place. The onset of pain is commonly delayed for a period of several hours. And, if the doctor who sees the swollen hand the next day does not take a careful history, he may attribute the condition to a soft-tissue infection.

Such a mistake will not be made if note is taken of the patient's occupation and of the absence of any marked local or systemic rise of temperature. The great importance of avoiding it lies in the fact that much of the tissue damage resulting from a grease-gun injury is due to ischaemia. Increasing the metabolic demands of the tissues by applying poultices or fomentations may determine a gangrene which could have been avoided.—I am, etc.,

London, W.C.1. RICHARD HARRISON.

Side-effects of Morphine

SIR,—The paper by Mr. G. Christie and his colleagues in your issue of March 22 (p. 675) on the treatment of certain side-effects of morphine is one of considerable interest. Nevertheless, I feel that to impute some of these side-effects to the liberation of histamine is to go beyond the evidence of their experiments. The hypothesis appears to rest solely on the control of vomiting induced by morphine by a weak antihistaminic agent, cyclizine chloride. They suggest that other side-effects including giddiness and pruritus might be due to histamine liberation.

Now it is plain that morphine-induced vomiting must be due to its action on some central mechanism in the nervous system. And, whatever might be the effects of antihistaminic agents on histamine liberated in the skin and other peripheral organs, it cannot be doubted that these drugs have a variety of action on the C.N.S. The precise site of their action is undecided, but much experimental evidence points to the brain-stem reticular system as being particularly sensitive to their influence. What pharmacological action the drugs used by Christie and his colleagues have upon brain-stem mechanisms I could not say. My own readings, so far, have not enabled me to discover any experiments concerning their actions on reticular structures. Should such experiments have been performed I hope that some reader will oblige me with the relevant information.

On the other hand, many other antihistaminic agents have been tested for their action on the brain-stem reticular substance, and it is obvious that their range of action is extremely wide. Many of them have predominantly atropine-like and anticholinergic properties, and it may well be that this action is of greater significance for the control of a variety of symptoms than are their antihistaminic virtues. There does not appear to be any close correlation between one property and the other.

Morphine is a well-known liberator of histamine. But whether its action on the C.N.S. is due to the liberation of histamine is not certain. Haley[1] mentions histamine as causing retching but not vomiting when injected intracisternally, an action shared by a considerable number of other drugs. Fazio and Sacchi[2] report that histamine can cause classic cataleptic symptoms in dogs when injected intracisternally but not if given by other parenteral routes. Histamine-liberating substances in general produce intense itching, a symptom which can be controlled by antihistaminic drugs. Intravenous histamine does not appear to produce this symptom. Intraventricular histamine also does not cause generalized pruritus.

Christie and his co-workers make little comment on the itching caused by morphine in their experimental subjects, but from their paper it is clear that the symptom was in no way alleviated by the drugs used for the control of vomiting and morphine narcosis. Evidence exists to suggest that morphine-induced pruritus is due to a central mechanism and not to the liberation of histamine at the periphery. Koenigstein[3] has shown that scratching paroxysms in the cat and dog can be caused by intracisternal morphine. Feldberg and Sherwood[4] have obtained similar reactions in cats when anticholinesterase drugs are injected intraventricularly. It has been suggested[5] that central itching in a variety of conditions is due to the inactivation of cholinesterase, a property strongly possessed by morphine. Macilwain[6] has suggested that many of the side-effects of morphine are due to its anticholinesterase activity.

To argue from animal experiments to explain human symptoms is often an invalid procedure. Nevertheless, the comment made by Christie and his colleagues that in their subjects the itching was experienced predominantly on the nose and the face has obvious parallels with the scratching of the muzzle area witnessed in cats subjected to intraventricular injection of anticholinesterase drugs. The hypothesis that central itching is caused by the accumulation of acetylcholine affecting the central reticular substance requires much more experimental proof before it can be accepted. From the evidence, however, one can find very little support for the concept that morphine-induced itching is caused by the liberation of histamine.

These criticisms in no way detract from the value of the paper as a whole. The knowledge that certain undesirable side-effects of morphine can be controlled by cyclizine chloride is of the greatest value. But I am not certain that the reasons given by the experimenters to explain their findings are necessarily correct.—I am, etc.,

London, S.E.5. F. A. WHITLOCK.

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"Diminished Responsibility" Manslaughter

SIR,—It is encouraging to see that Dr. W. A. O'Connor (*Journal*, March 29, p. 770) agrees with me that there is a difference between the effects of verdicts of "diminished responsibility" manslaughter and "guilty but insane" of murder. If I understand him correctly, however, he implies that the disposal of the "diminished responsibility" man is preferable to that of the "guilty but insane" murderer. He appears to try to give a spurious official authenticity to the odium-laden phrase "insane criminal" by putting it in inverted commas. In fact, the phrase "criminal lunatic" has not been officially used since 1948, when it was replaced by "Broadmoor patient." The use of the word "patient" firmly indicates the offender's status, with his *right* to all appropriate treatment, not, as Dr. O'Connor states, the doubtful likelihood of receiving the privilege of such treatment. Such patients, detained until Her Majesty's pleasure be known, are subject to constant review. The latest available figures, in the Ministry of Health's report for 1956,[1] show conditional discharges of Broadmoor patients to be 39% of the figures of admissions for that year.

Though my original letter (*Journal*, March 15, p. 641) was intended to emphasize the difference between the two verdicts under discussion, I am prepared to accept as my own the implied opinion that the "diminished responsibility" man should be specifically guaranteed investigation and, if possible, treatment of those factors which have led to his responsibility being diminished.—I am, etc.,

Crowthorne, Berks. PATRICK G. MCGRATH.

REFERENCE

[1] *Report of the Ministry of Health for the Year Ended 31st December, 1956*, Part I. Cmd. 293, 1957. H.M.S.O. London.

Carcinoma of the Breast

SIR,—I wish to comment upon the extraordinary leading article on carcinoma of the breast in your issue of February 1 (p. 269)—extraordinary because what in general is such sound advice is mixed with opinions and advice which are neither sound nor justified in our present understanding of this important disease.

There are many records of dramatic remissions brought about by the use of hormones, with ulcers healing, masses subsiding, and even widespread lung deposits resolving for a longer or shorter period. But to my knowledge no reputable person has ever claimed evidence that a beneficial hormone effect is other than transient, and all these patients die eventually from recurrence of disseminated cancer, an opinion with which your leader writer would undoubtedly agree. How, then, does he explain his advice that "oophorectomy may usually be prescribed for premenopausal patients"? Surely he does not believe that a disseminated tumour which cannot be perceived will respond better to hormone treatment than one which is detectable. In my opinion such advice is not only without scientific foundation but may be actively harmful in that all hormone treatment, whether the administration or deprivation of these substances, is preferably withheld until dissemination, otherwise unrelieved, becomes obvious. May I ask, too, on what grounds you advise, in the case of the woman who already has children, that "the prevention of pregnancy or its early termination if it has occurred is a wise course"?

In my experience of a radiotherapy department over a quarter of a century the youngest woman with breast cancer was aged 24 and she was not submitted to oophorectomy. For over four years she had disseminated lung deposits in which the year-to-year change was practically imperceptible until her disease became more active and she died with wide dissemination. Another of my patients had radical amputation of a breast followed by deep *x*-ray therapy for carcinoma. She subsequently bore two apparently healthy children which she suckled from the remaining breast. Eight years after her original amputation she died from disseminated deposits which must surely have lain dormant through two pregnancies and lactation periods. Another such woman lived five years after her operation before dying from deposits, having borne a child two years after this operation. Would you support the odd proposition that these two would have lived longer had the pregnancies been prevented? A few such cases do not teach us much about this grave malady, but they should teach us that it is dangerous to dogmatize from insecure premises.

My last complaint is that for the possibly curable case radiotherapy is relegated to a lowly position, and indeed by inference is classed below hormone treatment for such patients. Surely this is strange in a country which has established modern radiotherapy and which still leads the world in this specialty in spite of a vigorous world-wide missionary campaign. I could not agree more heartily that proper surgery is the primary and most important treatment for breast cancer. But, Sir, there are many patients in the world with long symptom-free survival after radiotherapy for this condition without surgery from one cause or another. I myself have a patient symptom-free over 10 years after radiotherapy for a histologically proved skin deposit, and the bigger and better centres in the United Kingdom will undoubtedly have many more such. It would be surprising indeed if the salvage from the clinically "early" cases were not greater when good radiotherapy is added to good surgery. In conclusion, may I express my conviction that, knowing so pitifully little about cancer, it is important that we do not promulgate false doctrine, particularly in so respected a publication as the *British Medical Journal*?—I am, etc.,

Adelaide, S. Australia. B. S. HANSON.

Delivery of the Placenta

SIR,—I would like to confirm the observation of Dr. Dora J. A. Clark (*Journal*, March 22, p. 713) that putting the newborn babe into the mother's arms will cause the uterus to contract and expel the placenta. When caesarean section is performed under spinal or extradural analgesia with the patient conscious, if the infant immediately on removal is shown to, and handled by, the mother, the uterus can be both seen and felt to contract. This simple expedient will prevent undue haemorrhage and also will serve to distract the mother's mind from the operation.—I am, etc.,

London, W.1. MASSEY DAWKINS.

SIR,—"Seldom does the accoucheur or supervising attendant have any idea where the placenta is . . ." writes Dr. R. B. Conyngham (*Journal*, March 8, p. 583). The lengthening of the cord outside the vulva by several inches is, as everybody knows, the best evidence that the placenta has passed into the vagina.

I always kept at hand, boiled and ready with my other instruments, a stainless steel safety-pin. The moment the baby was born I gently pulled out the slack of the cord and clipped the safety pin to it, close to the vulva. This was done in a moment and any subsequent lengthening was obvious, without the need to keep my eye glued to the cord. *Ten Teachers*[1] recommends tying a knot in the cord close to the vulva. But I submit that the safety-pin is better. I have never seen this method described in print, nor come across any doctor or midwife who used it, so venture to describe it now.—I am, etc.,

Crowthorne. EDWARD CHAPMAN.

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Psychopathic Personality

SIR,—What may be called "the elephant school" of psychiatry (*Journal*, January 25, p. 219) is quite futile. If we refuse to define what we are talking about, although it may be quite clear to ourselves, no one else can have a proper idea of the basis of discussion. Dr. C. E. Hedgeman Turner's definition of psychopathic personality (*Journal*, March 22, p. 710) is a gallant one. However, I would suggest that psychopathic personality be defined as a disease of personality, leading to antisocial behaviour, unresponsive to punishment. I have found it sometimes responds to

psychotherapy. One of my patients was a young man who had been thrown out of the Royal Navy and the Army for misconduct, who held up a taxi-driver with a pistol, and who took pot shots at station lights while passing in a train. I presume most people would accept him as being psychopathic. He came from a broken home, and with a year's psychotherapy changed into a responsible citizen who has behaved properly and not fallen foul of the police since.

Many psychopaths seem to me to be undeveloped schizophrenics and some never had any affection in childhood. Some appear to suffer from psychosexual abnormality. No doubt these illnesses have a common origin. I think that psychopaths need individual investigation, and it is improbable that those schools of psychiatric thought which devote their time to gathering statistics will make much progress with their elucidation.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

SIR,—May I be permitted to define a psychopath? I submit that he is a person who presents a character deformity whereby the clinical entity is an egoist and a social misfit who lacks foresight, is non-constructive and emotionally immature, and is basically anti-social. In a word, a character who has not outgrown the selfish behaviours and demands of childhood—a person who is constantly at war with society, either knowingly or unknowingly, depending upon his intellectual advance or retardation. A sheep in a lion's skin behaving like a jackal.—I am, etc.,

Retford, Nottinghamshire. JAMES A. ROE.

Problems of Puberty

SIR,—Dr. Douglas Hubble's article (*Journal*, January 25, p. 191) shows a distressing fallacious trend in modern materialistic medicine. He condones masturbation and homosexual activity by youths as being normal, and advocates heterosexual licence for adolescents. I agree with him that the urge is normal—but so is the urge to take what one wants, be it a loaf of bread, a diamond ring, or another man's wife, and to kill if necessary in order to do so. Perhaps the "conventions of our society" will soon accept theft and murder as being normal, and therefore not requiring restraint.—I am, etc.,

Portarlington, Australia. L. D. RENOUF.

The Stiff-man Syndrome

SIR,—I was interested to read the paper on "The Stiff-man Syndrome" by Drs. T. M. L. Price and E. N. Allott in the *Journal* of March 22 (p. 682). In spite of many chemical investigations, calcium analysis does not seem to be done; nor in the variety of treatments used empirically does parathormone or corticotrophin seem to have been tried. Phosphorus metabolism was reported to have been abnormal.—I am, etc.,

London, W.1. J. D. REDMILL.

Long-acting Sulphonamides

SIR,—Recently several sulphonamide compounds have been introduced to practitioners. Various claims have been made for these substances, the chief being that only once-daily dosage is required. It is suggested that they may be effective for long-term prophylaxis against streptococcal infections—e.g., in cases of acute rheumatism or in known rheumatic heart disease—to reduce the risk of bacterial endocarditis. Recent experience leads me to suggest that in clinical practice these drugs may not be effective.

In four cases of scarlet fever in different families I treated all the family contacts with sulphamethoxypyridazine ("lederkyn"), except for several infants too young to swallow tablets; these latter children received suspension sulphamezathine. In each of these families at least one of the contacts developed scarlet fever, and two mothers had acute pharyngitis with pyrexia. These cases occurred 4 to 11 days after the contact and in three of them sulphamethoxypyridazine was being taken at the time. In the other three cases it had been discontinued after 7 days—i.e., one to three days before the onset. None of the contacts who received sulphamezathine were infected.

In view of these cases I did not think it justified to continue using sulphamethoxypyridazine as a prophylactic, so that statistically my results may lack significance because of the small numbers concerned. It is, however, an experience worth noting, and suggests further clinical trials with this drug before it can be claimed to provide the known protection afforded by sulphamezathine and sulphadiazine against streptococcal infections.—I am, etc.,

Newcastle upon Tyne. A. J. WATSON.

Tetanus

SIR,—I have read with interest the letters of Dr. W. A. Hanna (*Journal*, February 22, p. 460) and Drs. H. A. Reid, D. P. Bowler, and L. T. Scott (*Journal*, March 29, p. 773) in which they further draw attention to the difficulty of assessing any method of treatment in tetanus. While I agree that many cases of tetanus must have died from oversedation, I feel that this has been largely the result of inadequate medical and nursing care. In areas where the incidence is high, it is well-nigh impossible to give the individual attention which is so necessary in the proper treatment of tetanus. To withdraw sedation altogether in these circumstances would certainly increase the suffering and probably not decrease the mortality. In the present state of knowledge the most effective means of reducing the mortality from tetanus lies in reducing the incidence by prophylactic immunization.—I am, etc.,

Stromness, Orkney. D. D. JOHNSTONE.

Aphthous Ulcers

SIR,—Drs. S. C. Truelove and R. M. Morris-Owen are to be congratulated on evolving a simple and effective treatment for this troublesome group of disorders (*Journal*, March 15, p. 603). In this area a large number of these patients are referred for dermatological advice. A few drops of ½ or 1% hydrocortisone in saline or as a skin lotion applied three or four times a day has proved effective in all but the most severe cases, which have been well controlled with the addition of tab. hydrocortison., 5 mg., dissolved in the mouth at bedtime. The success of such relatively inefficient methods confirms the experience of Drs. Truelove and Morris-Owen.

Patients with the minor form frequently volunteer that emotional upsets precede attacks, many of which can be aborted by applying hydrocortisone lotion. Inert lotion base often has an equally good effect. I would suggest that a trial of inert tablets for the maintenance dosage suggested by the authors might be illuminating. Before attempting suppression of such mucosal lesions with hydrocortisone, it is well to exclude underlying systemic causes and to recall that such lesions may be a manifestation of the pemphigus group of disorders.—I am, etc.,

Stoke-on-Trent. E. M. DONALDSON.

Industrial Dermatitis

SIR,—Like Dr. Bentley Phillips (*Journal*, March 8, p. 583) I also was surprised that Dr. Edward Collier (*Journal*, February 15, p. 396) had no cases of sensitization dermatitis following the use of acriflavine, proflavine, and penicillin on his workpeople. My experience in Sheffield (*Journal*, January 25, p. 199) was quite different, and I think that the explanation must be the close supervision of the workers attending the ambulance rooms in Dr. Collier's factories. It is quite evident from his letter in your issue of April 5 (p. 831) that the medicaments are applied for a very short time. The development of sensitization dermatitis depends on several factors, the most important being contact with the sensitizing substance. The more prolonged this period of contact, the more likely is sensitization to occur. In Dr. Collier's treatment centres, not only will the substances be discontinued as soon as the wound has healed, or as soon as

it is evident that the medicament is not promoting healing, but the area is also cleaned with 1% cetrimide, and this may help to reduce the penetration of flavine compounds into the epidermis. It is therefore probable that none of his workpeople have had these substances in contact with the skin for a sufficient length of time for sensitization to be established.

Many of the cases I described occurred in small factories with no proper continuous medical supervision. Some of the workmen had treated themselves with a flavine preparation obtained either from an "ambulance box" or from the chemist's shop. Dermatologists see only too frequently cases of dermatitis arising as a result of the use of flavine and penicillin in the treatment of trivial injuries sustained in the home.

It is therefore reasonable for these preparations to be used only in factories in which there is strict medical supervision, although in my experience the wounds heal as quickly, or even more quickly, following cleansing with 1% cetrimide alone. In factories without medical supervision and in home use such preparations are dangerous and may give rise to dermatitis which may incapacitate the unfortunate individual for months or even years.

It would be of interest to know how many cases of industrial dermatitis Dr. Collier sees in his factories in the course of one year and whether any of these occur within four weeks of a trivial injury, whether treated in the ambulance room or not.—I am, etc.,

Oxford. H. R. VICKERS.

Abnormal Responses to Muscle Relaxants

SIR,—Dr. P. B. Croft does anaesthesia a service by drawing attention to a myopathy associated with bronchial carcinoma (*Journal*, January 25, p. 181). Unfortunately, the amount and nature of the evidence presented makes it difficult to share his conviction that these patients were abnormally sensitive to muscle relaxants.

Whether the various clinical pictures presented have a common origin is impossible to say; one might be explained as the neurological sequelae of hypotension during anaesthesia (Case 4), others on the neuromuscular effects of barbiturates (Cases 1, 2, 3, and 5). Since Dr. Croft made no mention of this latter possibility, it should be pointed out that in every case where he would incriminate a relaxant thiopentone was also used. The extensive work of Sirnes[1] leaves little doubt that barbiturates in clinical doses may have an effect on skeletal muscle that is not easily opposed by neostigmine. Thiopentone, perhaps on account of its lipoid solubility, seems to be particularly active both at the myoneural junction and on the muscle fibre itself.[2] Barbiturates may also interfere with the nutrition of muscle.[3]

Thiopentone has abnormal paralytic effects on skeletal muscle in at least two conditions; porphyria[4 5] and dystrophia myotonia.[6] Might these presently reported cases not indicate a third disease where thiobarbiturates are dangerous (cf. the first operation of Case 3)? Further, it would be of interest to know whether these patients received the ubiquitous sedative barbiturate during their pre-operative days. In this way might the stage have been set for three of the fatalities whose *coup de grâce* was a shot of thiopentone.—I am, etc.,

Bellville, S. Africa. P. A. FOSTER.

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Research Workers and Pre-registration Year

SIR,—Dr. M. C. ffrench-Constant (*Journal*, March 29, p. 773) says that it would be infamous to waive the pre-registration year for full-time research workers qualifying in medicine. Education for a medical degree is not only a vocational training but also an academic study of human biology and pathology. It is surely in the interest of the medical profession to encourage preclinical research workers and teachers to have the training which helps them understand the problems and needs of clinicians. It is illogical to make training and experience for a career in research dependent upon vocational training such as is provided by the pre-registration year.

Dr. ffrench-Constant's fear of half-fledged doctors practising medicine is unnecessary; responsible people know their limitations. A psychiatrist does not undertake a gastrectomy, though the law may allow it. There is more danger in the fully fledged doctor thinking he could treat the diseases produced by the new weapons of destruction without the guidance of the research workers whom Dr. ffrench-Constant holds in contempt.—I am, etc.,

Cardiff. JULIA FOURMAN.

First Tuberculosis Dispensary

SIR,—The historical study of institutions involves burrowing into original sources to bring to light material discovered. Within this discipline, we wrote to you (*Journal*, February 8, p. 339) proposing precedence for the tuberculosis dispensary established in June, 1848, at 6, Liverpool Street, London. We called into question traditional claims to priority made for the Bank Street dispensary founded in Edinburgh in 1887, and the Talbot Road, Paddington, dispensary opened in London in 1909. A wall plaque at 13, Bank Street, Edinburgh, unveiled on July 26, 1957, in memory of Sir Robert Philip, repeats the assertion that he "founded a tuberculosis dispensary. The first clinic in the world dedicated to fighting a disease. . . ."

Apparently, to Dr. Lissant Cox (*Journal*, February 15, p. 402) and Dr. Harley Williams (*Journal*, March 1, p. 519) it matters not at all when, where, or in what circumstances early seeds of progress were planted. Fruit and flower are all they will acknowledge. Dr. Cox goes so far as to deny that prevention entered into the scheme of things before 1887.

Dr. A. R. Robertson's reference (*Journal*, March 1, p. 519) to a "Phthisical Dispensary" said to have been founded in March, 1805, at 70, Chancery Lane is a braver contribution. Granville[1] in his "Report on the Practice of Midwifery at the Westminster General Dispensary during 1818," published in the following year, avers that "there are 23 dispensaries besides hospitals and other medical charities in London. Some few of them, however, exist but nominally while others possess only limited means of affording relief in cases of sickness." His list does not mention any "Phthisical Dispensary," but it does include the "Public Dispensary" established in 1782 and operating at Bishop's Court, Chancery Lane. This was a general, not a special, dispensary and appears in a list, in volume 4 (1834) of the *London Medical and Surgical Journal*,[2] of metropolitan medical schools whose certificates of attendance qualified their holders for the Apothecaries' Hall diploma.

In the thirteenth edition (1820) of Reece's[3] *The Medical Guide*, this author refers to "the Phthisical Dispensary established in 1805 under the patronage of His Majesty at 170, Piccadilly, the author attends every Wednesday and Friday from 12 to 2 o'clock to give his advice gratuitously to consumptive patients recommended by a housekeeper as a proper object of charity." It is clearly manifest from other statements in this book that the premises referred to comprised in fact a pharmacy ("Chemical and Medical Hall") at which drugs and health publications were on sale to the public. A "Catalogue of Drugs (in English) eighth edition price 2s. 6d." was advertised in this volume as available at "Reece and Co.: Medical Hall, 170, Piccadilly." This "Phthisical Dispensary," we are reluctantly compelled to conclude, falls within Granville's description of those dispensaries which at that time "exist but nominally."

Dr. Lissant Cox's insistence that a "preventive outlook" did not exist at the older dispensaries but was first thought of at the Bank Street, Edinburgh, dispensary in 1887 wears a bit thin in the face of the statement in Highmore's[4] *Pietas Londinensis* (1810) that the expressed purpose of the newly established Bloomsbury Dispensary in 1801 included: "among the advantages to be expected from this institution are . . . preventing the extention and fatality of infectious diseases." Late eighteenth and early nineteenth century London dispensaries were more sturdy and enlightened medical centres than is generally realized or acknowledged.

Tuberculosis was recognized to be an infectious disease long before Koch discovered the bacillus. Mr. P. J. Bishop's reference (*Journal*, March 15, p. 647) to the "West London Dispensary for Diseases of the Chest" is indeed interesting. Davidson and Rouvray,[3] in their book *The Brompton Hospital*, from which Mr. Bishop was quoting, say "we have no record of the date at which this dispensary came into being, or the circumstances which led to its foundation." We are satisfied that London was foremost in the establishment of tuberculosis dispensaries.—We are, etc.,

London, S.E.1. W. HARTSTON.
London, E.2. W. F. WHEELER.

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5 Davidson M., and Rouvray, F. G., *The Brompton Hospital*. Lloyd-Luke, London, 1954.

Radio-isotope Test of Blood Flow

SIR,—It was welcome to see Mr. D. N. Walder's article (*Journal*, February 1, p. 255) on isotope tests in peripheral vascular disease. Its merits are undoubtedly that it is easy to do and can be used to examine muscle blood-flow during exercise, this latter being difficult to do by other means. The results are fairly consistent and the curves obtained are often repeatable. We have used his method both before and after amnion implantation, and found the results most useful.

In clinically unilateral claudicants bilateral isotope tests have been done and poor circulation has been found in the leg at fault, but also sometimes a deficient flow in the unsuspected or "good" leg. There is one observation we have not been able to assess—namely, the influence of the patients' "good" or "bad" days on the clearance curve. We have observed a correlation between isotope curves and clinical findings, and improvement in the isotope curves has been noted and found to compare with an improved clinical condition. The improvement in the clearance curves has been analysed on a statistical basis and found to be significant. However, we consider that more work is essential in elucidating the sodium clearance test by correlating it before and after treatment by plethysmography.—We are, etc.,

E. TROENSEGAARD-HANSEN.
London, W.C.2. N. W. RAMSEY.

Amnion Implantation in Peripheral Vascular Disease

SIR,—Different observers have reported varied results in the treatment of intermittent claudication by amniotic implants. May it be that they are using different portions of the membrane, some the caul, others the basal parts, for distinct properties have been attributed to the caul? My first teacher of anatomy—the late Professor J. Kay Jamieson—mentioned that in the folklore of some northern seafaring communities there was a notion that a child born with a caul would not succumb subsequently to drowning. While this may be just an old wives' tale, we ought not to dismiss it on this account. Whoever would have thought a few years ago that the use by peasants of cow-dung poultices for sores was anything but a dirty habit? But now with our knowledge of moulds we have a scientific explanation for their use.

Even if we ignore the mystic qualities of the caul, unknown chemical factors may exist in it; an implant of amnion may give back something to the male which he has lost or supply a substance in which he is deficient, for we have to explain the fundamental fact that atherosclerosis, which causes nearly all cases of intermittent claudication, is at least four times as common in men as in women. I suggest that those observers who have reported good results with amniotic implants might obtain similar results by giving the amnion as a suppository.—I am, etc.,

Leeds, 1. H. S. SHUCKSMITH.

Ski-ing Accidents

SIR,—I write on behalf of the Ski Accident Prevention Committee of the Ski Club of Great Britain. We have been concerned by the apathy and even antagonism of some members of the ski-ing public towards the use of release bindings. A preliminary analysis of the ski-ing accidents on which claims were paid by one insurance company (for the 1956–7 season) provides some interesting facts for the sceptics.

(i) Total accident claims paid—180.
(ii) Of these, 148 replied to our questionary (148=82% sample).
(iii) Of these, 59 were using some form of release binding (59=39%).
(iv) Of these, 27 sustained injuries unrelated to their release binding—e.g., collisions, etc. (59−27=32=22%).
(v) Of these 32, 15 admitted improper adjustment of their bindings (32−15=17=11%).
(vi) Of these 17, in 10 cases the release operated and only a minor accident—e.g., sprain—resulted at an average cost of £9 10s. (17−10=7=5%).
(vii) Of these 7 accidents, only two were fully protected by both forward and rotational release bindings. Average cost of these 7 was £30.
(viii) Average cost of all injuries irrespective of cause when wearing release bindings—£21; average cost of all injuries irrespective of cause when not wearing release bindings—£43.
(ix) Percentages of 1st season, 2nd to 3rd season, 4th to 5th season, and over 6th season skiers wearing release bindings were respectively 1.6, 15.3, 28.6, and 54.5. From these figures it is obvious that the more experienced skier realizes the value of release bindings.
(x) In no instance does the wearer of a release binding directly blame it in any way at all for the accident.

—I am, etc.,

London, S.W.1. J. HOWKINS,
Chairman, Ski Accident Prevention Committee, Ski Club of Great Britain.

Knock-knee in Children

SIR,—The letters of Dr. J. S. Dunbar (*Journal*, March 29, p. 774) and Mr. C. C. McKellar (*Journal*, February 22, p. 463) set out the present difference of opinion. Dr. Dunbar is on the side of those who maintain that knock-knee in children needs no treatment because it always rights itself spontaneously. Mr. McKellar points out the difficulties that may arise in convincing of this a mother who is acutely conscious of her own knock-knees. Observations with bearings on this, and on the related subject of bow-legs, may be made on any bathing beach.—I am, etc.,

London, W.1. DENIS BROWNE.

Rheumatology as a Whole-time Specialty

SIR,—Dr. M. M. Dobson (*Journal*, March 29, p. 776) deplores the fact that rheumatology is not recognized as a whole-time specialty. It is only in the N.H.S. that the need for special diagnostic and treatment facilities for this large group of patients has not yet been recognized.

The universities are more enlightened; Manchester and London have both instituted a chair in rheumatology, and several others maintain senior lectureships in this subject on their academic staff. The Royal College of Physicians has also reported that rheumatology should be recognized as one of the smaller specialties of general medicine, and that special research and treatment centres should be established in the regions.—I am, etc.,

London, W.1. W. S. C. COPEMAN.

POINTS FROM LETTERS

Post-influenzal Depression

Dr. G. A. SCHMEIDLER, Ph.D. (General Manager, Camden Chemical Co. Ltd.), writes: With reference to Dr. L. A. Nichols's note (*Journal*, April 5, p. 833), whereas, chemically speaking, methylpentynol is an unsaturated alcohol, ethyl alcohol is a saturated alcohol. The organic chemist recognizes distinct differences between these, and it is highly probable that the physiologist does too.

Obituary

W. H. McMULLEN, O.B.E., M.B., F.R.C.S.

Mr. W. H. McMullen, consulting ophthalmic surgeon to Charing Cross Hospital and consulting surgeon to Moorfields, Westminster, and Central Eye Hospital, died suddenly on April 15, aged 81.

William Halliburton McMullen was born in London on July 19, 1876, the son of Dr. William McMullen, who practised in South London. From the City of London School he went on to King's College, where he won junior and second-year scholarships as a medical student, and where he worked for a time as assistant demonstrator of physiology and prosector. He continued his clinical training at King's College Hospital, qualifying in 1898 and graduating M.B., B.S. (with honours) two years later. After holding the posts of junior and senior house-physician at his own teaching hospital, he took the F.R.C.S. in 1900 and became house-surgeon at the Royal Westminster Ophthalmic Hospital, later being appointed pathologist and curator at the same hospital. His first honorary appointment was as assistant ophthalmic surgeon to the Miller General Hospital, and he remained on the staff there for many years, becoming consultant surgeon on his retirement. Not long afterwards he joined the staff of the Royal Westminster Ophthalmic Hospital as assistant surgeon, finally retiring from the active staff in 1936.

Mr. McMullen became well known as an ophthalmic surgeon in London in the days before the first world war. In addition to the hospital appointments already mentioned he was for eight years ophthalmic surgeon to the Hospital for Sick Children, and from 1919 to 1923 he held a similar appointment at the Royal Northern Hospital. He was also lecturer in ophthalmology at the Charing Cross Hospital Medical School, and he joined the honorary staff of that hospital in 1929.

During the first world war Mr. McMullen was ophthalmic specialist to the Central London Recruitment Depot, and for his services was appointed O.B.E. in 1918, and during the last war he held an appointment in the E.M.S. President of the Section of Ophthalmology at the Royal Society of Medicine in 1937–8, he was also at one time a vice-president of the Ophthalmological Society of Great Britain. He wrote many papers on ophthalmological subjects, and among those he contributed to this *Journal* were reports on migraine and squint.

In 1906 Mr. McMullen married Kate Constance, daughter of G. Randell Higgins, who survives him.

Mr. G. G. PENMAN writes: By the sudden death of Mr. W. N. McMullen we lose another of the distinguished band of ophthalmologists who led this branch of the profession between the two wars. Those of us who worked with him will always remember him as a very skilful surgeon, to whom nothing was too much trouble, a most acute diagnostician, and as one possessing a fund of learning and experience which was always at the service of his colleagues and assistants. He was most kind, gentle, and painstaking with his patients, who were devoted to him and were very sad when he gave up first hospital and then private practice.

As senior surgeon of the Royal Westminster Ophthalmic Hospital he was a wise counsellor and leader, whose advice and help were always most valuable, especially during the planning, and actual making in 1928, of the move from the old hospital next door to Charing Cross to the new building in what was then Broad Street, Holborn. After his retirement from the active consultant staff he continued until very recently on the committee of management (house committee after the amalgamation with Moorfields). He enjoyed these meetings very much, meeting old friends and keeping in touch with the hospital, but the other day said that he thought that the time had come to give them up. An original member of the Faculty of Ophthalmologists, he took a prominent part in their deliberations.

He was very fond of landscape sketching in water colour or pencil, but was very modest about his achievements. It gave him countless hours of pleasure and private satisfaction, and the results always met with admiration when he could be persuaded to show them to knowledgeable strangers. But he would never exhibit his work in public. Up till 1939 he enjoyed a game of golf, and was a member of the Oxhey Golf Club.

He leaves a widow and three sons, to whom we extend our sincerest sympathy in their grievous loss.

A memorial service for the late Mr. W. H. McMullen will be held at St. John's Wood Chapel, London, N.W.8, on Wednesday, May 7, at 11 a.m.

F. H. LACEY, T.D., M.D., F.R.C.O.G.

Dr. F. H. Lacey, honorary consulting gynaecologist to the Manchester United Hospitals, died at his home at Balcombe, near Haywards Heath, Sussex, on April 11. He was 78 years of age.

Frank Hamilton Lacey was born on May 2, 1879, the son of Dr. Thomas Samuel Lacey, who was in general practice near Oldham, and, later, in Manchester, and from whom he derived the touch of Irish in his blood which made him such a witty and bright companion. His mother was Miss Langton, of Langton Hall, Lincolnshire, a direct descendant of Bennet Langton, the friend of Dr. Samuel Johnson, and from her he inherited letters and other memorials of the great lexicographer. Lacey received his medical education at Manchester University, graduating M.B., Ch.B. in 1906, proceeding to the M.D. in 1912. Soon after graduation he became a house-surgeon at St. Mary's Hospital, Manchester, and in 1908, after holding house-surgeon posts elsewhere, succeeded William Fletcher Shaw as senior resident officer, which exacting post he held for four years, and so had a clinical training second to none. His active connexion with St. Mary's—as registrar, assistant, and full honorary surgeon—continued to his retirement in 1946, being broken only for four years by the first world war, in which he served in Egypt and the Dardanelles with the R.A.S.C., which he had joined as a Territorial before the war, and, later, in France with the R.A.M.C., to which he had transferred, retiring with the rank of major. Subsequently, he was awarded the Territorial Decoration. While away at the war he was appointed gynaecologist to Withington Hospital, one of the two large workhouse hospitals in Manchester. When these hospitals were handed over to the corporation, he transferred to Crumpsall, where he remained in charge of the obstetrics and gynaecological unit until his retirement from practice. Later he also became honorary gynaecologist to the Christie Hospital for Cancer and clinical lecturer in obstetrics and gynaecology in the University of Manchester. When the Royal College of Obstetricians and Gynaecologists was founded in 1929 he was elected one of the foundation Fellows. In the same year he served as a vice-president of the Section of Obstetrics and Gynaecology of the British Medical Association when the Association held its Annual Meeting at Manchester. He did not publish many papers, but was a regular attender at the meetings of the North of England Obstetrical and Gynaecological Society, taking his full share in the discussions and serving as president in 1932.

We are indebted to Sir WILLIAM FLETCHER SHAW for the following appreciation: The news of Frank Lacey's sudden death on April 11 greatly shocked his many old friends who had met him only that afternoon at a party given by the Royal College of Obstetricians and Gynaecologists to celebrate my 80th birthday, which, as one of my oldest friends, he insisted upon attending despite increasing illness and almost complete blindness. He thoroughly enjoyed meeting again so many old friends, and we have the memory of a bright happy face as he moved from one to another.

Lacey was well versed in the science and art of obstetrics and gynaecology, and his opinion was much sought after. In his hospital and teaching posts he could always be relied upon to pull his full weight and never to shirk his duties,

no matter how onerous they might be. It was such as he who made and kept the voluntary hospital service what it was, the passing of which many now regret. What his old friends cherish is the memory of his bright, cheerful personality, with his absolute loyalty to friends and hospitals. No matter what knocks adversity brought his way—and he was no more immune than anyone else, one of the worst being a detached retina when a student, which was always a serious handicap to his operative work—he always showed a smiling face and never groused. He was one of the few who did not criticize colleagues behind their backs, even when others might have thought their actions deserved it, and he could always be relied upon to support anything for the welfare of his hospitals and profession. In 1946, when he retired from his hospitals, he bought a small farm near Crawley, and when this was commandeered for the new town he moved to another at Balcombe.

During the first world war Frank Lacey married Miss Evelyn Rudge, of Wallasey, who has been such a wonderful support to him during some years of failing health and increasing blindness. She survives him, with two sons and one daughter, to all of whom we extend our sympathy.

G. F. BARBOUR SIMPSON, M.D., F.R.C.P.Ed. F.R.C.S.Ed.

Dr. G. F. Barbour Simpson, consulting gynaecologist to the Western Dispensary, Edinburgh, died at his home in Edinburgh on April 8 after many months of slowly increasing weakness. He was 83 years of age.

George Freeland Barbour Simpson was born at Edinburgh on September 21, 1874, the second son of Sir Alexander Russell Simpson, professor of midwifery and the diseases of women in the University of Edinburgh, and the grand-nephew of the great Professor Sir James Young Simpson, so that he was born into a distinguished obstetrical heritage. Moreover, his middle names derived from his mother's side, she being a sister of Dr. A. H. Freeland Barbour, who became the lecturer on gynaecology in the university, and was, with Dr. Berry Hart, the author of a textbook on gynaecology which had a great and deserved reputation in those days.

Barbour Simpson was educated at George Watson's College and at the University of Edinburgh, where he graduated M.B., Ch.B. in 1898. After the customary year or two of clinical training in hospital internships at the Royal Infirmary and the Royal Maternity Hospital, and later a period of postgraduate study in Paris, he began to devote himself exclusively to midwifery and gynaecology. He became university assistant to his father and subsequently to his successor in the chair, Sir John Halliday Croom. During these early years he became a Fellow of the Royal College of Surgeons of Edinburgh (1903) and Physicians (1905); proceeded to the M.D. degree with a thesis on fibroid tumours of the vagina; was appointed an assistant physician to the Royal Maternity and Simpson Memorial Hospital; and became a Fellow of the Obstetrical Society of Edinburgh. In his university post Simpson proved himself an excellent teacher, and when in due course he demitted the office he became an independent lecturer in the then famous "extra-mural" school of medicine of the Royal Colleges. For several years he served the university as an extern examiner, and for many years he examined for the triple qualification. He was elected a Fellow of the Royal Society of Edinburgh in 1908 and became vice-president of the Obstetrical Society in 1913. In 1905 Simpson was admitted a member of the King's Bodyguard in Scotland, the Royal Company of Archers; and during the first world war he joined the R.A.M.C., in which he rose to the rank of major. For some time he acted as second-in-command of the Officers' Hospital at Eaton Hall, under his friend and fellow-specialist, Lieutenant-Colonel (later Sir) Ewen Maclean.

Simpson was not a prolific writer, and, apart from two or three papers to the Obstetrical Society, his major contribution was the *Edinburgh Stereoscopic Atlas of Obstetrics* (1908), in the preparation of which he was assisted by the late Dr. Edward Burnet. This was a good piece of work which afforded proof—if such were needed—of the superiority of stereoscopic views of anatomical subjects over flat projections. But he was a man of wide interests, and in 1923 these led him to enter the town council of Edinburgh. This step involved the virtual relinquishment of his professional career in medicine, but for a period of twelve years he rendered good public service on the council, passing through the offices of bailie and police judge and the convenorship of the hospitals committee, among others. He retired from the town council in 1935 and subsequently devoted a good deal of his attention to the affairs of the Royal College of Physicians, to which he acted as treasurer for twelve years. In private life Barbour Simpson was a man of many friends and strong social instincts. He was devoted to open-air sports, shooting, and in particular to fishing. He was one of the founders and the first secretary of that band of enthusiastic anglers, the Edinburgh Medical Angling Club.

To his widow, his son, and his two daughters sincere sympathy is offered.—R. W. J.

E. J. BRADLEY, *M.C.*, M.D., F.R.C.S.Ed.

Mr. E. J. Bradley, formerly surgeon to the Margate General Hospital, died at Bournemouth on March 22. He was 67 years of age.

Edwin John Bradley, the second son of the late Edwin Bradley, J.P., of Dover, was born on July 16, 1890. Educated at Dover College, where he became head prefect, he went on to Jesus College, Cambridge, and St. Bartholomew's Hospital, qualifying in 1913. In the following year he obtained the degrees of M.B., B.Chir., and proceeded M.D. in 1921. He held resident posts at Bart's and the Bristol General Hospital, and then served as a major in the R.A.M.C. in Egypt and France throughout the first world war, gaining the M.C. and bar and being mentioned in dispatches. In 1919 he started general practice in partnership with Dr. A. E. Hodder at Stafford. Five years later he obtained the Edinburgh F.R.C.S. and became a surgeon to the Staffordshire General Infirmary. He married in 1929, and on account of his wife's health moved to Margate, where he was at once appointed as surgeon on the staff of the General Hospital. From 1945 until his retirement because of ill-health in 1948 he was president of the hospital. He was medical officer to the Royal School for Deaf and Dumb Children and to the local Home Guard during the second world war.

T. S. S. writes: Jack Bradley was extremely kind to me when I joined him in practice at Margate in 1935. I soon realized how generally beloved he was and how difficult it would be to live up to his high standard, for he exemplified what really good doctoring should be. His patients gave him their absolute trust and confidence, and still, after many years, remember him with the greatest affection. As his occasional anaesthetist I became very impressed by his skill as a general surgeon, particularly by his imperturbability at moments of crisis, and when, later, I served with him on hospital committees, his calm common sense was equally impressive. He never spared himself when patients needed him, and the nursing staff at Margate still talk of how he operated for days and nights on end during the Dunkirk evacuation. An all-round athlete at school, Jack Bradley played rugger in the Jesus, Bart's, and United Hospitals fifteens, but his health, first affected by gas while serving with the 1/3 North Midland Field Ambulance in 1918, suffered further by stress of surgical work and single-handed practice during the second world war. The onset of polyarthritis on top of chronic bronchiectasis unhappily forced him to give up first surgery and then general practice. It was typical of him that seeking occupational therapy for stiffening fingers he should turn to the making of books in Braille. For many years a keen member of Rotary, he was president of the Margate club in 1939. Gardening and stamp collecting were his hobbies, and despite increasing crippling he continued his practical interest in greenhouse plants to

the end. He was deeply religious, and, though naturally reticent, this showed in every aspect of his daily life. Just one example was his adoption in 1938 of two refugee boys from Hitler's Germany. In 1955–6 his three talks in the B.B.C.'s "Silver Lining" programme—entitled "The Temptations of a Long Illness," "Compensations," and "Facing up to Pain"—were an inspiration to other sufferers. His religious faith as well as his wife's devoted care must have fortified him greatly during his long and painful illness. All who came into contact with Jack Bradley knew him to be a thoroughly good man.

Medico-Legal

ABUSE OF LEGAL AID

[FROM OUR LEGAL CORRESPONDENT]

On March 20 Mr. Justice Roxburgh, in giving judgment against a legally aided plaintiff in an action in the Chancery Division, said that there ought to be some way of stopping a legally aided case which was boosted up by false evidence, and his Lordship knew of no means of doing so (*The Times*, March 21). This had been an action for nuisance, and the plaintiff, a deaf old man of 81, had given false evidence and put faked exhibits before the court. He ordered him to pay the costs of the action, but suspended payment until further order.

The difficulty is, of course, to know whether evidence is false or exhibits faked until the evidence has been given in court and tested by cross-examination and until the exhibits have been put in in court and subjected to critical scrutiny. No reputable lawyer would allow his client, whether legally aided or not, to put forward through him a case supported by what he knew to be false evidence and faked exhibits. With a legally aided client it is his duty, if he comes to the conclusion that there is no case, and still more if he sees that false evidence is being relied on, to bring the matter to the Legal Aid area committee for the legal aid certificate to be revoked. This is not seldom done.

If it is only before the court that the falsity of the case becomes apparent the remedy is in the judge's hands. If at the close of the plaintiff's case he is satisfied that the plaintiff has not established a prima facie case—for example, because it depends on the plaintiff's evidence and the plaintiff is such a manifest liar that his evidence is not to be relied on—the judge can throw the case out without calling on the defence. A jury can stop a case in similar circumstances. Similarly when a defendant is obviously unreliable and the defence depends on his evidence the judge, having heard his evidence, is always entitled to say, "I don't believe a word he says," and even with the most long-winded counsel such Draconian measures cut the rest of the business pretty short.

The harm done by speculative actions and false cases to innocent defendants is not a creature of legal aid and is nothing new. The only difference the legal aid scheme has made is that the lawyers who act for the impecunious plaintiff do not have to look to him for their remuneration, but to the legal aid fund. On the assumption that all lawyers are reputable, this difference should make no difference.

DOCTORS CHARGED AT TOWER BRIDGE

At Tower Bridge Court on April 16 further charges were brought in connexion with the case of Miss Jean Cook, the Australian nurse whose death was the subject of an inquest last month (*Journal*, March 29, p. 778). As a result Dr. Ellis Stungo and Dr. Louis Newton, who had been arrested on warrants the day previously, were remanded on bail until May 1.

Dr. Newton was charged with unlawfully killing Miss Cook, and with unlawfully using an instrument with intent to procure her miscarriage. Dr. Stungo was charged with counselling and procuring Dr. Newton to procure the miscarriage of Miss Cook. Mr. Geoffrey Howe, for the defence, said: "The charges are completely denied and the case will be most strenuously defended" (*The Times*, April 17).

At the Old Bailey the trial of Dr. Louis Newton, committed on a coroner's inquisition on a charge of Miss Cook's manslaughter (*see Journal*, March 29, p. 778), was put over to the May session.

Medical Notes in Parliament

STATEMENT ON SENIOR REGISTRARS

The MINISTER OF HEALTH announced on April 21 that the Joint Consultants Committee and he had agreed to set up a joint working party to study, in the light of experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organized. He continued:

I have concluded that—pending and without prejudice to the working party's report—the current arrangements for senior registrar posts should be modified in certain respects, in view of the fact that some senior registrars have long completed the normal tenure of their posts but have not yet succeeded in obtaining a higher post. I am satisfied that these senior registrars should be given an opportunity of remaining in the hospital service whilst they continue to compete for higher posts, and hospital boards are being asked where necessary to offer extended contracts pending the working party's report.

Also without prejudice to the working party's report, I am asking hospital boards to submit proposals for designating a limited number of senior registrar posts—mainly from among those already existing—which will provide responsible work commensurate with that which is normally expected of a fourth-year senior registrar; will carry a higher rate of pay; will offer security of tenure; and will be available to senior registrars who have completed the normal period of appointment in the grade. The senior registrars selected for these posts will of course be free to continue to compete for higher appointments. I will emphasize to boards that these senior registrar posts are not to be regarded as a substitute for additional consultant posts.

The Secretary of State for Scotland is discussing with the Scottish Joint Consultants Committee the application of these arrangements to Scotland.

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) said these interim arrangements appeared at first sight to be a satisfactory solution to the short-term problem, but the only tolerable solution for the long-term problem would be a considerable expansion of consultant posts. Was it necessary to set up a working party to come to that obvious conclusion? Mr. WALKER-SMITH said regard must be had to the fact that the number of consultant posts desirable had to be looked at in the light of staffing structure and economic context. He hoped for a quick and valuable report from the working party, and preferred to wait for it.

Sir KEITH JOSEPH (Leeds, North-east, Con.) said he welcomed the constructive solution to this intractable and complex problem, without prejudice, as the Minister had said, to the recommendations of the working party. He asked the Minister to note that it was not commonly accepted that the only long-term solution was the expansion of the consultant force. The economics of the service to the public and the location of consultants in relation to the public demand for them must be examined most carefully. Mr. WALKER-SMITH said he would bear the suggestions in mind.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) said all the Minister had said was that the matter was to be postponed once more, and that the anxiety of these senior registrars was to continue for an indefinite period. These men were being offered excellent opportunities in the United States, and if there was going to be another postponement Britain would lose some of its best doctors. Mr. WALKER-SMITH said he did not think Dr. Summerskill could have heard his reply, or else she did not understand it. What he had said indicated that there was a good deal more for the senior registrar than she thought.

CHANGES IN OPTICIANS BILL

The Opticians Bill passed its concluding stages in the Commons on April 18, and was read the third time.

Clause 18 (The Companies Committee) was amended to provide that this committee, to advise the General Optical Council on matters relating to bodies corporate carrying on business as ophthalmic or dispensing opticians, should include "at least one" (not just one) person appearing to the Council to represent the interests of each of these sections.

Reference of Patients to Medical Practitioners

On Clause 25 (Miscellaneous matters on which rules may be made), a new subsection (3) was inserted, as follows:

(3) The General Optical Council shall as soon as practicable after the day appointed for the coming into operation of this section make and submit to the Privy Council rules providing that where it appears to a registered optician that a person consulting him is suffering from an injury or disease of the eye, the optician shall, except in an emergency or where that person is consulting him for the purpose of being given treatment in accordance with rules under paragraph (*d*) of subsection (1) of this section or in such other cases as may be prescribed, being cases in which it is, owing to special circumstances, impracticable or inexpedient to do so, take the prescribed steps to refer that person to a registered medical practitioner for advice and treatment.

Mr. R. RUSSELL (Wembley, South, Con.), who moved it on behalf of the promoters, said it was designed to emphasize, at the behest of the medical profession, that opticians accepted certain limitations on other functions. It stated that it was the duty of the optician, if he detected any indication of disease, to refer the patient immediately to a medical practitioner. It was to emphasize that this was the accepted fact in the profession that he moved the amendment. Mr. SOMERVILLE HASTINGS (Barking, Lab.) thanked the promoters for the addition of the subsection, and said that members of the medical profession who felt strongly about this would be grateful to them.

On the Schedule (Constitution, etc., of the General Optical Council), the number of registered medical practitioners on the Council was increased from five to six, of whom four instead of three are to be nominated by the Faculty of Ophthalmologists.

Vice-Admiral J. HUGHES-HALLETT (Croydon, North-East, Con.) said he withdrew corresponding amendments during the committee stage, because at that time no agreement had been reached between the B.M.A. and the ophthalmic opticians concerning the matter, and it appeared that if the amendments were then carried the opticians would move for a corresponding addition to their representation, and there would be an ever-growing Council. The B.M.A. had also made the point that if there were to be only three, one of whom had to come from Scotland, there might be difficulties in ensuring that medical questions were adequately covered. Since the committee stage, he was informed, agreement had been reached. Mr. RUSSELL emphasized that the amendment had been accepted by the ophthalmic opticians with considerable reluctance. They hoped that as a result there would be no further opposition from the B.M.A. to the Bill. Mr. HASTINGS, expressing his pleasure at the acceptance of the amendment, said that doctors were watching with interest and enthusiasm the development of the ophthalmic opticians as a learned profession, and felt that in this development the medical profession could be of assistance.

Parliamentary Secretary's Summing Up

Mr. RICHARD THOMPSON, Parliamentary Secretary to the Ministry of Health, summed up on the third reading the major changes that had been made in the Bill during its passage, and which he said had left it in much better shape than when it was introduced. The Bill now provided that the register of ophthalmic opticians should be in two parts, those proposing to test sight only, and those proposing to test sight and dispense glasses. This gave effect to what the Crook Committee had in mind. In Clause 20 (Restrictions on testing of sight), amendments had been accepted which prohibited the testing of sight except by a registered medical practitioner or a registered ophthalmic optician. In Clause 21 (Restrictions on sale and supply of optical appliances), there was a prohibition on sales except by or under the supervision of a registered doctor or optician. Clause 25, as amended that day, defined the scope of the optician's work in relation to that of the medical practitioner. It was vitally important that the optician should not overstep the boundary between his functions and those of the doctor. He was glad that the opticians as a profession were in agreement with this provision. The amendment had been carefully considered, and should provide an excellent basis on which the General Optical Council could work. They could look forward to a constructive partnership between the opticians and the doctors as a result of the Bill.

There were some 8,000 ophthalmic opticians and 800 dispensing opticians in the United Kingdom, Mr. Thompson continued. They gave over 5½ million sight tests a year, and dispensed just under 5 million pairs of glasses under the Health Service alone. The Government expected the General Optical Council to give a lead to the best professional and trading standards, and to do it more effectively by being allowed a reasonable latitude in the process.

OVERSEAS PENSIONS AND LEARNED SOCIETIES

In his budget speech on April 15, before his major proposals, Mr. D. HEATHCOAT AMORY mentioned a number of minor ones which, he said, would improve the tax system. Among them were proposals affecting tax relief for overseas pensions and for subscriptions to professional societies. The Chancellor said:

"Another minor improvement which follows assurances given by my right hon. Friend the Secretary of State for the Colonies is a proposal to give tax relief in certain circumstances on pensions for overseas service becoming payable under the Overseas Service Act.

"I am proposing in the Finance Bill to meet one point that has been pressed upon me in connexion with the Schedule E expenses rule. This will enable some deduction to be claimed in respect of subscriptions to professional societies with activities relating to an employee's work and for certain statutory registration fees. It will cost £¼m. in the first year and £1m. in a full year."

ANSWERS TO QUESTIONS

Poliomyelitis Vaccine Supplies

Mr. WALKER-SMITH, answering several questions about the supply of poliomyelitis vaccine on April 21, said the Government's current programme for vaccination against poliomyelitis involved the vaccination of those in the priority groups—mainly children under 15 and expectant mothers—who registered for it. For this purpose both British vaccine and Salk were used and initial orders for 5,000 litres of Salk were placed last September so that with a reasonable regularity of delivery steady and uninterrupted progress would be maintained in the vaccination programme.

There had, however, been some interruption of supplies to local health authorities, and consequently of the vaccination programme, for a number of causes. These delays in the delivery of vaccine had occurred in each of the four original sources of supply, two British firms, one Canadian, and one in the U.S.A. In each of the four cases the cause of delay was different. But in no case was it within the control of or due to the fault of the Government.

Immediate steps had been taken to remedy the deficiencies. Earlier this year when the difficulties in the supply of British vaccine occurred 2,800 litres of further Salk vaccine were ordered and further new purchases were immediately initiated to replace the Salk vaccine due to have been delivered last week.

Any delay in vaccination due to shortage of vaccine was, of course, something which they all keenly regretted, but they would do their utmost to minimize it. A batch of British vaccine was now in process of distribution; a further batch would be distributed before the end of the

week, and, barring further unforeseen difficulties, much larger supplies, mainly of Salk, would become available next month. He was arranging for the purchase of further substantial quantities of Salk vaccine, and expected to be in a position to give some further information as to this, and also the supply position and prospects, next week.

He also stated that in Great Britain at the end of February, the latest date for which detailed information was available, approximately 3 million persons, the great majority of them children, required vaccination with two injections and a further 650,000 with one injection. Some 6½ million doses were therefore required, towards which 2 million were then in the hands of the local health authorities. Detailed figures for the end of April would become available next month.

National Laboratories

Mr. SOMERVILLE HASTINGS asked whether, in view of the need for poliomyelitis vaccine and the failure, both of the United States and of private enterprise, to supply this need fully, the Minister would make the necessary provision in national laboratories. Mr. WALKER-SMITH said he was not sure exactly what provision Mr. Hastings had in mind. If, however, he was referring to the actual manufacture of vaccine, he did not think the suggestion would be of any help, and clearly could not affect the present supply position.

Short-term Rise in Radioactivity

Mr. R. MASON (Barnsley, Lab.) asked the Prime Minister on April 15 to state the extent to which there had been an increase in atmospheric radiation over this country after the recent series of Russian nuclear tests, and to what extent there had been a noticeable increase of strontium-90 in the Welsh mountains, the Scottish Highlands, and the Pennines. Mr. H. MACMILLAN: There was a significant rise in short-term radioactivity in the upper atmosphere late in March which may have been produced by Russian tests. This short-term activity was not dangerous. The level of strontium-90 is monitored regularly and the results made available to the House from time to time.

The PRIME MINISTER, in a reply to a question on April 17 by Mr. W. HAMILTON (West Fife, Lab.) about this short-term rise said that short-term increases of radioactivity of comparable magnitude had been observed before, but there was nothing to suggest that they occurred at regular calendar intervals. He must make it clear that the levels of activity returned to about the normal background values after a few weeks.

British Tests

Mr. S. SWINGLER (Newcastle-under-Lyne, Central, Lab.) asked on April 15 what increase in radioactivity over Britain was expected as a result of the forthcoming series of British nuclear tests. Mr. MACMILLAN said that tests of the type held by the United Kingdom did not contribute significantly to the level of atmospheric radioactivity in the United Kingdom or elsewhere.

Mr. SWINGLER said that it was very difficult to reconcile statements such as that with statements constantly reported from reputable physicists on both sides of the Atlantic about inevitable increases in the incidence of leukaemia and bone cancer arising from the accumulation of nuclear tests. Could they not have from the Government's scientific advisers some firm information, and whether the Prime Minister was right or Dr. Condon was right? Mr. MACMILLAN thought one of the confusions might arise from the form of the question, which was about radioactivity. The character, type, and size of any further British tests were of such a kind that he was advised there would be a negligible increase in total radiation.

Mr. S. SILVERMAN (Nelson and Colne, Lab.) said that when the Medical Research Council reported in 1956 it had experience of the explosions of only four megaton bombs. Up to date more than 50 had been exploded. In 1956 the Medical Research Council gave a percentage that was regarded as dangerous, and which had not then been reached. There was now considerable scientific evidence to show that the percentage had since been exceeded. If there was now doubt about the scientific facts, would the Prime Minister get the information up to date, and bring to an end this damnable conspiracy of silence? Mr. MACMILLAN said he was advised by the Medical Research Council that in its view no detectable increase in the incidence of leukaemia or bone cancer was to be expected from the nuclear explosions that had taken place up to now.

Vital Statistics

Secondary Case of Smallpox

On the evening of April 14 a 2-year-old boy was admitted to the Liverpool Regional Hospital Board's isolation hospital at New Ferry, Bebington, with clinically typical smallpox. His home is about half a mile (0.8 km.) due west of the hospital. The onset of the boy's illness was on April 6; three days later a slight rash on the body appeared, and by the next day it was generalized. The boy had not been vaccinated. It was to this same hospital that a Lascar seaman with smallpox was admitted from the s.s. *Circassia* on March 20 (see *Journal*, March 29, p. 779), and, although the route of spread is at present obscure, the boy's infection is thought to be secondary to the Lascar's. The point has been made that the prevailing wind during the critical period was from the north-east—from the hospital to the boy's home—and weather conditions were particularly dry. Bebington has a population of around 50,000, and with memories of an outbreak of smallpox there in 1946 and the constant reminder of the isolation hospital the vaccination state is said to be well above the national average, and at the moment no mass vaccination campaign is contemplated. The boy's family are confined to their home, his unvaccinated 7-year-old sister and the other members of the family have been vaccinated, and they are being inspected twice daily. All the other known direct contacts —some 25 persons—are under daily surveillance and have been offered vaccination, which nearly all have been glad to accept.

Week Ending April 12

The largest variations in the number of notifications of infectious diseases in England and Wales during the week ending April 12 were rises of 901 for measles, from 4,165 to 5,066, 51 for acute pneumonia, from 534 to 585, and falls of 247 for dysentery, from 1,110 to 863, 119 for scarlet fever, from 857 to 738, 44 for food-poisoning, from 156 to 112, and 20 for whooping-cough, from 515 to 495.

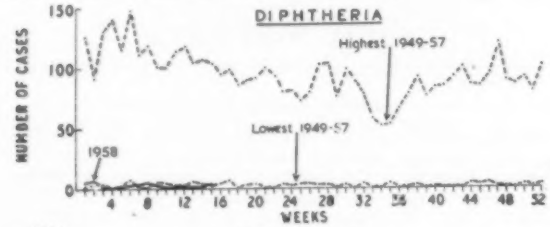
The largest rises in the incidence of measles were 156 in Devonshire, from 131 to 287 (Exeter C.B. 105), 147 in Leicestershire, from 177 to 324 (Leicester C.B. 214), 72 in Lancashire, from 390 to 462 (Liverpool C.B. 150), and the largest fall was 65 in Glamorganshire, from 264 to 199. Only small fluctuations were reported in the local returns of whooping-cough. The largest fall in the number of notifications of scarlet fever was 28 in Essex, from 110 to 82. Four cases of diphtheria were notified during the week, being 2 more than in the preceding week.

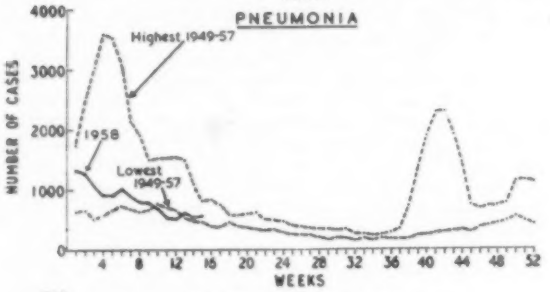
Eleven cases of acute poliomyelitis were notified: these were 2 more for non-paralytic and the same number for paralytic cases as in the preceding week. The only area with 2 cases was Daventry M.B.

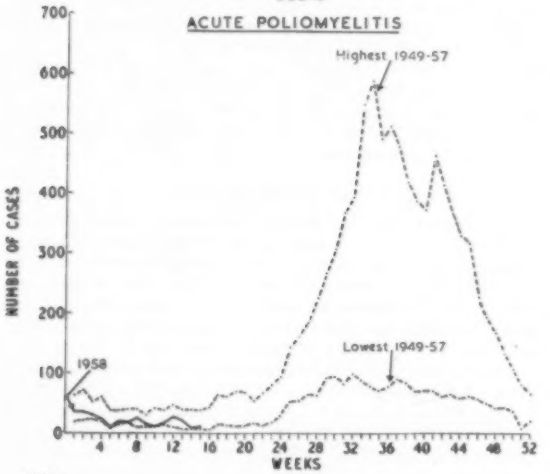
The largest falls in the notifications of dysentery were 146 in Yorkshire West Riding, 48 in London, and 47 in Lancashire. The chief centres of infection during the week were Lancashire with 271 cases (Manchester C.B. 74, Oldham C.B. 65, Liverpool C.B. 51, Lancaster M.B. 10); Yorkshire West Riding 154 (Sheffield C.B. 32, Huddersfield C.B. 21, Leeds C.B. 16, Hemsworth R.D. 13), London 71 (Islington 12, Shoreditch 11), Cheshire 48 (Wallasey C.B. 20, Northwich R.D. 17), Nottinghamshire 47 (Worksop M.B. 24), Gloucestershire 33 (Bristol C.B. 27), Middlesex 30, Durham 23, and Essex 20 (Thurrock U.D. 12).

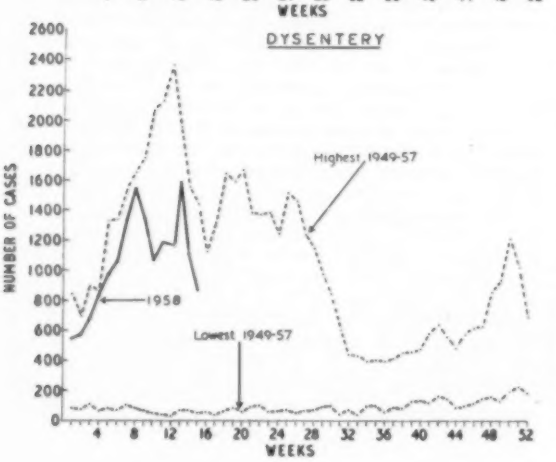
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 5** (No. 14) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	2	0		9	1	2	0	2
Dysentery ..	1,110	119	180	12	18	1,051	36	252	11	4
Encephalitis, acute	6	0		0		4	1		0	
Enteric fever:										
Typhoid ..	5	0	0	0		2	0	0	0	
Paratyphoid ..	0	0	1(B)	0	1(B)	3	0	4(B)	0	1(B)
Food-poisoning ..	156	14	17	0		204	32	44	0	
Infective enteritis or diarrhoea under 2 years				7	19				10	16
Measles*	4,165	250	113	26	10	25,280	2007	308	354	277
Meningococcal infection	22	3	17	2	3	29	2	13	1	
Ophthalmia neonatorum	35	35	4	0		32	1	4	0	
Pneumonia† ..	534	43	233	25	4	466	25	212	6	2
Poliomyelitis, acute:										
Paralytic ..	9	1	0	0		17	2	3	0	2
Non-paralytic ..	0	0				20	2			
Puerperal fever§ ..	161	18	5	1		204	33	15	1	
Scarlet fever ..	857	54	62	33	22	878	68	84	52	24
Tuberculosis:										
Respiratory ..	466	47	140	13		583	76	274	24	
Non-respiratory	40	5	8	1		65	8	17	2	
Whooping-cough ..	515	30	37	7	16	2,768	137	263	7	67

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	* No comparable figures available.	0	0	0	1
Dysentery ..	1	0		0			0		0	
Encephalitis, acute		0			0		1			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	2	0	3		0	0	0	0
Influenza	46	3	6	1	0		1	1	0	1
Measles		0	0	0	0		1	0	0	0
Meningococcal infection		0	2				0	0		
Pneumonia ..	761	64	38	16	7		37	0	21	13
Poliomyelitis, acute	4	0		0	0		0			0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	95	5	2	3	0		7	8	2	3
Non-respiratory		0	0	0	0		0	0	0	1
Whooping-cough ..	0	0	0	0	0		0	0	0	0
Deaths 0–1 year ..	324	27	28	7			24	29	6	23
Deaths (excluding stillbirths) ..	11,374	892	680	134	153		708	603	107	174
LIVE BIRTHS ..	13,395	1112	935	249	341		1264	1086	233	369
STILLBIRTHS ..	312	20	20				37	30		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Royal College of Surgeons.—At a meeting of the council on April 17 Professor R. B. KERR, professor of medicine in the University of British Columbia, was appointed a Sir Arthur Sims Commonwealth travelling professor to visit Britain and parts of Africa in 1959; Professor E. J. WAYNE, Regius professor of the practice of medicine, Glasgow University, was similarly appointed to tour Canada in 1959. It was agreed to establish a Court of Anaesthesia in the College, and the council expressed their thanks to the British Oxygen Company Ltd. for a gift for this purpose. The Jacksonian prize for 1957 was awarded to Mr. B. B. MILSTEIN, F.R.C.S., and the subject for the 1959 prize chosen—"Non-specific Granulomata of the Alimentary Tract." The following, being practitioners of twenty years' standing, were elected fellows of the College without examination: Professor R. W. SCARFF, Air Vice-Marshal J. C. NEELY, Mr. GEORGE BELL, Mr. G. H. THOMAS, Professor F. C. WILKINSON, and Professor A. E. GALLOWAY.

Chair of Virology at Glasgow.—Dr. M. G. P. STOKER, lecturer in special pathology at Cambridge, has been elected to the new chair of virology at Glasgow University. He will take up his appointment on October 1. As was announced last year (*Journal*, May 4, 1957, p. 1071), the Scottish Hospital Endowments Research Trust has provided £225,000 for the building, equipping, and initial running expenses of a building for the new department. Dr. STOKER graduated M.B., B.Chir., Cambridge in 1942, proceeding M.D. in 1947. He is a fellow of Clare College, where he is director of medical studies.

Australian National University.—Dr. F. C. COURTICE, an Australian, has been appointed as the first occupant of the chair of experimental pathology in the John Curtin School of Medical Research, Canberra. After graduating B.Sc. at Sydney, Dr. Courtice came to Oxford in 1933 on a Rhodes scholarship, and there gained a D.Phil. He then qualified from the London Hospital, returning in 1937 to Oxford as a Beit fellow and later a Nuffield research fellow. During the war Dr. Courtice carried out research on chemical warfare at the Chemical Research Station; after the war he was appointed reader in human physiology at Oxford. In 1948 he returned to Australia as director of the Kanematsu Memorial Institute of Pathology, Sydney. Dr. Courtice will take up his duties in Canberra on July 1.

Obstetric Research Unit.—On April 22 the chairman of the Scottish Hospitals Endowments Research Trust, Sir JOHN ERSKINE, opened new accommodation for the Medical Research Council's Obstetric Medicine Research Unit at Aberdeen. This takes the form of an additional story to the antenatal wing of Aberdeen Maternity Hospital. The cost has been met by a grant of £60,000 to Aberdeen University from the Scottish Hospitals Endowments Research Trust, and the North-eastern Regional Hospital Board (Scotland) is equipping and furnishing the clinical accommodation and providing the nursing staff. The Obstetric Medicine Research Unit was established in 1954, under Professor DUGALD BAIRD, from a nucleus of research workers who had been investigating problems of pregnancy and childbirth under his direction in the University Department of Midwifery, where the Unit has since been housed.

Group for Research on Steroids.—The Medical Research Council, with the Board of Governors of the United Sheffield Hospitals, is establishing in Sheffield a Group for Research on the Chemical Pathology of Steroids. The Group's director will be Dr. J. K. NORYMBERSKI, who for the last few years has been directing research, supported by the Board, on steroids in rheumatoid arthritis. The work of the new Group, however, will be concerned with the study of steroids in disordered metabolism generally. The Board is providing accommodation for the Group at the Jessop Hospital for Women and also one-third of the Group's annual cost. The Board of Governors has received two grants, each of £4,000, from the British Empire Cancer Campaign and the Sheffield and District Convalescent and Hospital Services Council, to meet the costs of altering the premises and equipping the laboratories.

New Rheumatology Journal.—The American Rheumatism Association has launched an official journal—*Arthritis and Rheumatism*. The first issue is dated February, 1958, and the journal will appear bimonthly. The editor is Dr. WILLIAM S. CLARK, with his editorial offices at 2035, Abington Road, Cleveland 6, Ohio; the publishers are Messrs. Grune and Stratton, Inc., 381, Fourth Avenue, New York; subscription rates outside the U.S.A. are $2.50 for single copies, $11 annually; Messrs. Baillière, Tindall and Cox, Ltd., 7 and 8, Henrietta Street, London, W.C.2, are the agents in Great Britain. The first issue has 98 text pages. *Arthritis and Rheumatism* is intended primarily for reporting the results of original research. In a footnote to Dr. Clark's inaugural editorial it is stated that the journal is perceived as being "international in scope as it concerns both reader and contributor."

Soviet Journals.—Starting in May, Consultants Bureau Inc., of 227, West 17th Street, New York, will issue a monthly contents list of the 39 Soviet scientific and technical journals at present being translated into English. *Express Contents of Soviet Journals*, as this guide will be called, will include journals translated by other private agencies beside Consultants Bureau and by scientific societies. The annual subscription rate is $25.

The May issue of *Express Contents* will include all January–February, 1958, Russian issues received by Consultant Bureau by March 30, 1958; the June issue will include all March–April material (received by April 30), and so on; so that a 1958 subscription will cover all Tables of Contents to the 1958 calendar year Russian issues. A separate volume, *1957 Contents*, which will include all 1957 issues of the 39 journals with which *Express Contents* begins, will be published in June, 1958, at $15. As a special introductory offer, Consultants Bureau will accept orders for the May, 1958, issue separately at $6, and will credit that amount against a 1958 subscription received from the same purchaser by June 30, 1958. A free sample issue containing representative Tables of Contents only is immediately available from the publisher on request. Among the 39 journals now covered are: *Bulletin of Experimental Biology and Medicine*; *Biophysics*; *Sechenov Journal of Physiology*; *Problems of Oncology; Problems of Virology; Journal of Microbiology, Epidemiology and Immunobiology; Problems of Hematology and Blood Transfusion; Microbiology; Doklady - Biological Sciences; Biochemistry; Doklady - Biochemistry; Pharmacology and Toxicology;* and *Soviet Journal of Atomic Energy*.

B.M.A. Film Library.—A copy of the following film has been presented to the Library by Dr. RAPANI KOSONEN, of Helsinki, "Life Goes on in Spite of Everything" (16 mm., black-and-white, sound, running time 22 minutes). It illustrates the treatment of respiratory paralysis and a system of glosso-pharyngeal breathing. The following films have been purchased by the Library:

"Post-Natal Exercises to Prevent Stress Incontinence" (16 mm., colour, silent, running time 7 minutes); made by Dr. C. K. Vartan; for students, midwives, patients, and doctors. "Closure of Foramen Ovale in Calf and Foal" (16 mm., black-and-white and colour, silent, running time 4 minutes); made at the Nuffield Institute for Medical Research, Oxford; for undergraduate, postgraduate, specialist, and consultant audiences. "Bits and Pieces" (16 mm., colour, silent, running time 20 minutes); made by Professor C. S. Russell, University of Sheffield; for students. "Action of Human Mitral and Aortic Valves" (16 mm., colour, silent, running time 12 minutes); made by Mr. I. K. R. McMillan; for undergraduate, postgraduate, and specialist and consultant audiences. "Lymphangiography" (16 mm., colour, silent, running time 10 minutes); made by Professor J. B. Kinmonth; for undergraduate, postgraduate, and specialist and consultant audiences. "Rehabilitation of the Double Leg Amputee" (16 mm., colour, silent, running time 13 minutes); made at the Southend-on-Sea Hospital; for all those interested in the field of rehabilitation.

Requests for these and other films from the Film Library should be addressed to the Secretary of the B.M.A.

Medical Film Catalogues.—*La Presse Médicale*, our distinguished French contemporary, has issued a 100-page supplement to its *Films Médicaux et Surgicaux Français*. The descriptions of the films are based on reviews which appeared originally in *La Presse Médicale*. The main catalogue (pp. 302) and the supplement, which is not sold separately, are obtainable from Masson et Cie, 120, Boulevard Saint-Germain, Paris, 6. Another recent film catalogue is that issued by the photographic department of St. Mary's Hospital Medical School (Praed Street, London, W.2). This catalogue, which may be obtained on request to the department, lists 14 medical films made at St. Mary's and available for hire to medical and allied audiences.

André Mayer Fellowships.—The Food and Agriculture Organization of the United Nations is offering 8 to 10 André Mayer fellowships this year. They will be awarded to persons with the highest qualifications for research in agriculture, agricultural economics and statistics, fisheries, forestry, or nutrition. Further information can be obtained from the secretariat of the F.A.O. National Committee for the United Kingdom, c/o Ministry of Agriculture, Fisheries, and Food, Whitehall Place (East Block), London, S.W.1.

COMING EVENTS

British Association of Physical Medicine.—Annual meeting, April 25 and 26, at the Royal Free Hospital, London, W.C.1.

Mental Health Exhibition.—Organized by Park Prewett Hospital, April 29 to May 3, at St. Peter's Hall, Hinton Road, Bournemouth.

Contraceptive Technique.—A lecture and demonstration by Mrs. MARIE STOPES, D.Sc., at the Mothers' Clinic, 108, Whitfield Street, London, W.1, May 1, at 2.30 p.m. Tickets free of charge from the clinic.

Study Course on W.H.O.—Coinciding with the Eleventh World Health Assembly, which is being held in Minneapolis, U.S.A., the World Federation of the United Nations Associations will hold there its customary study course on W.H.O., from May 26 to June 4. Further details from Mrs. Lawrence D. Steefel, 2808, West River Road, Minneapolis, 6, Minnesota, U.S.A.

Assises Françaises de Gynécologie. — "Problems of Puberty in Girls and their Management," May 26–28, Annecy. Details from Dr. R. SÉNÉCHAL, 31, rue Raynouard, Paris, 16.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 28

MANCHESTER MEDICAL SOCIETY.—(1) SECTION OF ODONTOLOGY: At Lecture Room, Dental Hospital of Manchester, 4.30 for 5 p.m., annual general meeting, followed by clinical meeting. (2) SECTION OF GENERAL PRACTICE: At Large Anatomy Theatre, Manchester University, 8.30 for 9 p.m., Dr. R. W. Burslem: Some Obstetric Difficulties.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Professor C. L. Oakley, F.R.S.: Sites of Production of Antibodies.

Tuesday, April 29

●BRITISH COUNCIL FOR REHABILITATION.—In the Great Hall, B.M.A. House, Tavistock Square, W.C., 4.30 p.m., annual general meeting, 5 p.m., First Dame Georgiana Buller Memorial Lecture by Sir Reginald Watson-Jones: Disability and the Restoration of Life.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Sir Arthur Gemmell: Some Episodes in Ovarian Surgery.

LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE.—5 p.m., Professor R. M. Titmuss: Health.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. H. G. H. Richards: Thrombosis.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHYSIOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Dr. B. Delisle Burns (McGill University): Responses of Neurones in the Cerebral Cortex to Polarization.

Wednesday, April 30

FOUNTAIN HOSPITAL.—5.30 p.m., film by Dr. E. J. Anthony: Aspects of Childhood Psychosis. Discussion to be opened by Dr. Mary W. Woodward.

GLASGOW ROYAL INFIRMARY.—At Lister Lecture Theatre, 5 p.m., Dr. John Macintyre Memorial Lecture by Professor B. W. Windeyer: John Macintyre: A Prophecy in Retrospect.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Laboratory Procedures for Mycotic Infections.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: Results of Antibacterial Treatment in Pulmonary Tuberculosis.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8 for 8.30 p.m., Miss Mabel Rew: Early Days.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At No. 1 Theatre, Clinical Sciences Building, York Place, 4 for 4.30 p.m., clinical meeting by Professor J. H. Kellgren, Dr. J. Sharp, and Staff of Rheumatism Research Department. Clinical demonstrations of rheumatoid disease as delimited by the sheep cell test.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Dr. Paul Weiss: Mechanism of Wound Healing.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. J. Ball: Some Pathological Aspects of Rheumatism.

ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF UROLOGY.—At Royal College of Surgeons of England, 5 p.m., Urology Lecture by Dr. M. Jaupitre: Le Cinema Endoscopique en Urologie: Technique Indication et Interêt.

Thursday, May 1

ALFRED ADLER MEDICAL SOCIETY.—At Royal Society of Medicine, 8 p.m., Professor Alexander Kennedy: Psychology of Training and Competitive Sport.

BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, Medical School, 4 p.m., Ingleby Lecture by Professor E. C. Amoroso, F.R.S.: Constitution of the Mammalian Placenta.

DUBLIN UNIVERSITY: TRINITY COLLEGE.—At Anatomy Theatre, 5 p.m., Montgomery Lecture on Ophthalmology by Professor A. Hagedoorn (Amsterdam): Gross and Minute Defects of the Germ Cells and Clinical Ophthalmology.

FACULTY OF HOMOEOPATHY.—5 p.m., Dr. R. A. F. Jack: Homoeopathy in a Rural Community.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—2.30 p.m., Institute At Home: at Royal College of Surgeons of England, 5.30 p.m., Professor W. D. M. Paton: Pharmacology of Mucous Membrane.

INSTITUTE OF PSYCHIATRY.—5 p.m., public lecture by Professor Delisle Burns (McGill University): Physiology of Amnesia.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Mr. R. G. Taylor: Use of Bone Grafts in Delayed and Non-union of Fractures.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION: PSYCHOTHERAPY AND SOCIAL PSYCHIATRY SECTION.—At Cheadle Royal Hospital, near Manchester, 4.30 p.m. Dr. G. C. Heller: Schisms in Psychotherapy. Open to members and their guests.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. M. A. Partridge: postgraduate demonstration in psychiatry.

SCIENTIFIC FILM ASSOCIATION.—At Royal Photographic Society, 7 p.m., Dr. Dubois de Montreynaud: Clinical Significance of New Types of Endoscope (Illustrated).

Friday, May 2

BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, Medical School, 4 p.m., Ingleby Lecture by Professor E. C. Amoroso, F.R.S.: Functional Role of the Placenta.

INSTITUTE OF DENTAL SURGERY, EASTMAN DENTAL HOSPITAL.—5 p.m., Dr. William Rakower (New York): Diagnosis in Oral Surgery.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. H. Meara: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: clinical demonstration.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Mr. H. J. Malkin: Breech Presentation.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. H. Haxton: Influence of Suture Materials and Methods on the Healing of Abdominal Wounds.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. T. B. Fitzgerald: Contraction Ring Dystocia.

●SOCIETY FOR PSYCHOSOMATIC RESEARCH.—At Royal College of Physicians of London (May 2-4), Conference on the Nature of Stress Disorder.

Saturday, May 3

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At West Kent General Hospital, Maidstone, 3 p.m., annual general meeting. Talk by Dr. P. N. Swift on his American journey.

Sunday, May 4

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., lecture-demonstration for general practitioners. Meet in front hall of main hospital building.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Gregor.—On April 2, 1958, at his home, 26, The Avenue, Hitchin, Herts, Edmund William Gregor, M.R.C.S., L.R.C.P., formerly of Melbourn, Cambs, aged 89.

Mackwood.—On April 5, 1958, at sea, John Charsley Mackwood, *M.C.*, M.R.C.S., L.R.C.P., of Budleigh Salterton, Devon.

Mitchell.—On March 31, 1958, Howard Edward Hall Mitchell, M.B., B.S., of Carshalton, Surrey, aged 77.

Nield-Faulkner.—On March 17, 1958, in Liverpool, Samuel Amery Nield-Faulkner, L.R.C.P.&S.Ed., L.R.F.P.S., of 29, Beechfield Avenue, Blackpool, Lancs.

Pollard.—On March 22, 1958, Herbert Dean Pollard, M.B., F.R.C.S., of 82, Clapham Road, Bedford.

Posner.—On April 2, 1958, at his home, Harrietsham, Kent, Richard Posner, M.D., D.P.H.

Stark.—On March 22, 1958, in hospital, Edinburgh, Joseph Stark, L.R.C.P.&S.Ed., L.R.F.P.S., late of 60, Leith Walk, Leith, Edinburgh.

Steele-Perkins.—On March 31, 1958, at Perhams, Honiton, Devon, Duncombe Steele Steele-Perkins, L.R.C.P.&S.Ed., L.R.F.P.S., aged 75.

Taylor.—On March 29, 1958, at 74, St. Michael's Road, Leeds, Headingley, Yorks, Robert Alexander Russell Taylor, M.B., Ch.M., F.R.C.S., M.R.C.O.G., D.M.R.T.

Vautier.—On March 30, 1958, at 10, Courtland Terrace, Merthyr Tydfil, Glam, Charles Keith John Vautier, M.B., M.R.C.P., D.C.H., D.M.R.D.

Vaux.—On March 18, 1958, at Northease Lodge, Rodmell, Lewes, Sussex, Francis Leonard Vaux, M.D., Lieutenant-Colonel, R.C.A.M.C. (retired).

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Cancer of Oesophagus

Q.—*What are the respective indications for surgery and radiotherapy in the treatment of cancer of the oesophagus? What is the operative mortality rate and the expectation of life in these treatments?*

A.—Surgery offers the best chance of relieving symptoms in cancer of the oesophagus. In a few cases long-term survival results. Radiotherapy is indicated in patients who are unfit for a major procedure and in those cases in which the growth is in the upper part of the thoracic oesophagus. Operation on a growth in this situation may entail too great a hazard.

Operative mortality, taking a liberal view of what is considered to be operable, is about 38% in major resections. In palliative short-circuit operations the mortality is about 25%. Although the operative survival for squamous-cell carcinoma is only 15 months and for adenocarcinoma 9 months,[1] statistics often give a false picture; in 6 patients the average operative survival period was 4 years 4 months and a further 5 patients are alive and well after intervals of 6 years, 5 years, 4 years, 4 years, and 3 years.[2]

The average survival period of a large series of patients treated by radiotherapy with 170 kV *x*-rays was 8 months. Using rotation therapy, and with the improved technique afforded by supervoltage *x*-rays, palliation can be achieved in a greater number of patients, but recurrent dysphagia is common and may be painful. If radiotherapy is used, it may be wise to carry out a preliminary intubation with a plastic tube, and probably the best hope for improvement in the prognosis is to be looked for in the combination of surgery and subsequent radiotherapy.

REFERENCES

[1] Cox, R., *Ann. roy. Coll. Surg. Engl.*, 1957, **21**, 133.
[2] Franklin, R. H., *Surgery of the Oesophagus*, 1952. Edward Arnold and Co., London.

Aetiology of Chronic Alcoholism

Q.—*What is known about the aetiology of chronic alcoholism? On what lines is current research on alcoholism proceeding?*

A.—Our knowledge of the aetiology of chronic alcoholism is very incomplete. It may be a symptom of other mental disorders—e.g., general paralysis of the insane, dementia or manic depressive psychosis, etc. In non-symptomatic cases a genetic factor may appear to be operating. Lemere *et al.*[1] report that 62.4% of 500 alcoholic cases had a positive family history of alcoholism, while in 200 cases of moderate drinkers 16% was the corresponding ratio. It might be said that, for unknown reasons, alcohol is more tempting and attractive to alcoholics than to moderate drinkers. Recent theories have been put forward that alcoholism is due to: (1) Hypoadrenocorticism showing itself in low blood sugar, low ketosteroids, etc. This may be only the result of damage to the adrenal by heavy alcohol consumption, however. (2) Metabolic disorder, in which the symptoms of alcoholism are due to the disruption of the enzyme systems in the brain, with consequent failure of the glucose oxidation chain. The current treatment of delirium tremens and acute alcoholic states by massive vitamin-B complex dosage is based on this view.

Attempts to define a type of personality prone to alcoholism have not been successful, the nearest approach to this being the finding that the alcoholic has less ability to construct neurotic defences against anxiety and he tends to "act out" his conflicts, rather than being able to repress them.

The research trends into alcoholism tend to be on the lines of: (1) Therapeutically orientated research studies, as in a few special units for the treatment of chronic alcoholics in this and other countries. (2) Pharmacological studies such as that being at present carried out by Professor G. C. Drew at Bristol University. His work is specially directed towards the effect of alcohol in relation to driving motor-cars. Professor Masserman, of Chicago, has done a considerable amount of work on the effects of alcohol in normal cats and in cats which had been made "neurotic." He found that, in certain circumstances and doses, alcohol could have a normalizing effect on the behaviour of the "neurotic" cats. On the other hand, in normal cats the effect of alcohol was to disrupt the more complex and recently learned patterns with small doses and progressively more disruptive effects with increasing dosage.

REFERENCE

[1] Lemere, F., Voegtlin, W. L., Broz, W. R., O'Hollaren, P., and Tupper, W. E., *Northw. Med. (Seattle)*, 1943, **42**, 110.

Post-herpetic Neuralgia

Q.—*What is the frequency of post-herpetic neuralgia following herpes zoster, and what is its usual prognosis?*

A.—Very few reliable figures are available on the incidence of post-herpetic neuralgia following zoster. Most authorities regard it as a somewhat rare sequela in the average case, though the incidence is undoubtedly higher in old people. Neuralgic pain is more commonly encountered in zoster of the trunk than when the trigeminal nerve is involved, in which case it is invariably the ophthalmic division which is involved. Post-herpetic neuralgia may continue for many weeks or even months; it is inclined to do so more often in old people than in the young or middle-aged. In cases where pain persists for an unduly long time it is advisable to look for associated or aggravating causes.

Stimulation of Vagus

Q.—*Why does stimulation of the vagus nerve inhibit the heart and at the same time overstimulate the gastrointestinal tract, causing colic?*

A.—If the stimulus applied to a nerve is strong enough to excite all of its component nerve fibres, impulses will pass to all parts of its distribution, which in the case of the vagus nerve includes both the heart and the gut.

The nature of the response of the effector organs supplied depends ultimately on the behaviour of each effector in the presence of the chemical transmitter liberated at the nerve endings. The parasympathetic division of the autonomic nervous system shares with the sympathetic the somewhat disturbing attribute of manifesting excitatory as well as inhibitory effects, because the response of the effector organ to the chemical transmitter (in the case of the parasympathetic system acetylcholine) may be either excitatory or inhibitory.

Strong stimulation of the right vagus will result in the liberation of acetylcholine in relation not only to the muscle of the gut but also to the sino-atrial node in the heart. In the former case it is excitatory and may produce ill-co-ordinated spasms of contraction as well as increased peristalsis. If the contractions are sufficiently severe the familiar pains of colic are produced. On the other hand, the excitable tissue in the heart, in this case the S.A. node, is inhibited with consequent slowing of the heart rate.

Active Immunization Against Herpes Zoster

Q.—*Are there any prospects of active immunization against herpes zoster?*

A.—The relationship between the viruses of varicella and zoster is so close that they can be considered together in this context. Many authorities now regard the two viruses as identical. Until recently it has not been possible to culture

either of them in the laboratory—a necessary prelude to active immunization—but a few years ago reports from America showed that the viruses of both varicella and zoster had been grown in tissue culture, though admittedly under rather difficult conditions. It seems probable that herpes zoster results either from reactivation of virus from previous exposure or is the result of an infective process in the partially immune subject. Under these conditions it would be more logical to immunize against varicella if there appeared to be justification for such a procedure. There seems little doubt now that the cutaneous lesions in zoster result from centrifugal spread of virus along nerve pathways.

Ascorbic Acid

Q.—*Can continuous doses of 200 mg. ascorbic acid three times daily cause any toxic effects?*

A.—No. There is no evidence of any toxic effect from doses of up to 1,000 mg. a day given over long periods of time.

Ventilation in Schools

Q.—*How often should the air in classrooms and dormitories in boarding schools be changed in order to minimize the risks of infection? What is the most practicable way of checking that this standardization of ventilation is being achieved?*

A.—Ventilation rates of four to six air changes per hour have commonly been recommended for schoolrooms, but these figures were based on the rate of air change needed to prevent accumulation of body odours rather than on the rate needed to prevent transfer of infection. There is very little information on the effectiveness of ventilation in controlling the spread of infection. In one recent study[1] the ventilation rate was measured repeatedly in the classrooms of six primary schools, and compared with the sickness absence rate. There was no evidence that the rooms with the greater rate of air change had a lower incidence of respiratory tract illness. It seems that, for the present, minimum ventilation rates can be specified only in terms of preventing discomfort and not in terms of preventing illness.

Ventilation rates are measured by liberating a tracer gas or vapour, such as hydrogen, carbon dioxide, nitrous oxide, or acetone, into the air and measuring the rate at which it disappears. There is no method that can be used without employing moderately elaborate apparatus.

REFERENCE

[1] Reid, D. D., Lidwell, O. M., and Williams, R. E. O., *J. Hyg. (Lond.)*, 1956, **54**, 524.

NOTES AND COMMENTS

Treatment of Paralysis Agitans.—Mr. R. C. W. LOWE, F.R.C.S.Ed. (Lund, Sweden), writes: Your answer under this heading does not appear to have taken into account the motive that perhaps underlay the question (*Journal*, March 15, p. 659) on progress in the treatment of paralysis agitans. News of recent advances in the treatment of such chronic maladies often reaches the patient by rumour or in magazine articles more rapidly than it can be conveyed by conventional means to their medical attendants. The advance the questioner had in mind may have been the increasing use of surgical methods in the treatment of this condition.

From 1938 onwards, sporadic surgical assaults upon the pyramidal tract in the mid-brain or the spinal cord met with indifferent success, often only at the expense of residual hemiparesis. During the past five years the development of stereotaxic methods in cerebral surgery at a number of clinics in Europe, the United States, and Japan has permitted surgical intervention in regions otherwise inaccessible. Small destructive lesions in the neighbourhood of the globus pallidus of the corpus striatum were found to depress or abolish the rigidity and tremor of Parkinsonism. Such lesions can be fashioned with remarkable accuracy and consistency without any undesirable effect, provided that a sufficient interval is allowed between operations on the two sides. Present techniques employ either alcohol injection or thermo-electric coagulation as the destructive agent. The former method is less certain and not without risk: the latter is safe and precise. Both may be supplanted by high-energy proton or ultrasonic beam techniques now being developed. Results were reported at the International Congress of Neurological Sciences in July, 1957, from several centres. One such report cites significant improvement in 80% of 60 patients treated by sub-pallidal thermo-electric tractotomy. Both tremor and rigidity were relieved in the majority, all of whom had been disabled for several years despite adequate medication with one or more of the drugs listed by your expert. Unilateral operation relieves the disability of the opposite upper limb and that of both lower limbs, so that gait and balance may be substantially improved. A number of problems associated with bilateral operation at this site remain to be overcome. Even so, patients with advanced bilateral disease have regained much useful function after a unilateral procedure.

The questioner specified "paralysis agitans," which, as described by Parkinson, is a pure disorder of motor function characterized by rigidity, tremor, and restriction of movement. This syndrome is relieved by operation. Symptoms such as drowsiness, oculogyric crises, and excessive salivation present in the post-encephalitic type of Parkinsonism are not influenced by surgical procedures. The motor syndrome, however, responds just as well to pallidotomy in post-encephalitic as in arteriopathic, hereditary, or metabolic forms of the disease. Arteriopathic patients with failing memory, confusion, or severely impaired sphincter control are not suitable subjects for surgery. Patients followed for periods up to five years have maintained the post-operative improvement. Nevertheless, pallidotomy is only a more potent form of symptomatic treatment, complementary to the use of hyoscine and the synthetic spasmolytic drugs, which can be reduced in dosage to tolerable levels. Unquestionably, however, it is a very significant advance in the treatment of a crippling and tragic disability.

Mastication and Digestion.—OUR EXPERT writes: Since replying to the question on mastication and digestion ("Any Questions?" February 22, p. 476) I have read the account of Mr. J. H. Farrell's important work.[1] Farrell conducted several hundred experiments on 29 commonly eaten foods. In each experiment a weighed sample of the food was chewed and another was left unchewed. Both samples were sewn into separate cotton-mesh bags and swallowed; such of the samples as remained were subsequently recovered, examined, and weighed. The residues from chewed specimens, when present, were small, but there were large residues of the unchewed samples of 18 foods, including samples of pork, beef, mutton, and various vegetables. These experiments demonstrate quite conclusively, and for the first time, that chewing is essential for complete digestion of many foods. Farrell, however, was not satisfied to leave the study there, and he conducted a further series of experiments to see how much chewing was necessary. Contrary to expectation, he found that the amount needed was very little and that subjects with what would be regarded as thoroughly inadequate dentition chewed their food sufficiently to secure complete digestion of the samples.

REFERENCE

[1] Farrell, J. H., *Brit. dent. J.*, 1956, **100**, 149.

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